ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 29 (O.S., Vol. XXXIII) JULY, 1948 NUMBER 1

CONTENTS

Subscription per volume or per annum, net postpaid, $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico; $8.00, other countries.

Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph 4, section 538, P. L. & R., authorized October 7, 1936.

ANNALS OF
INTERNAL MEDICINE

VOLUME 29 JULY, 1948 NUMBER 1

MODIFICATION OF FAT ABSORPTION IN THE DIGESTIVE TRACT BY THE USE OF AN EMULSIFYING AGENT *

By CHESTER M. JONES, M.D., F.A.C.P., PERRY J. CULVER, M.D., GLADYS D. DRUMMEY, B. S. and ANNA E. RYAN, B.A., *Boston, Massachusetts*

NUTRITIONAL disorders of clinical importance are due to a variety of factors. Thus malnutrition may be secondary to an inadequate food intake due to loss of appetite or to organic disease interfering with the ingestion of food. It may be caused by an abnormal increase in the metabolic requirements of the body, as in Graves' disease or in febrile states. It may be associated with an inadequate utilization of food absorbed from the digestive tract, as in diabetes or chronic severe hepatic disorders. Undernutrition may also be the result of a diminution in the absorptive powers of the small bowel, secondary to an intrinsic physiological disturbance or to a reduction of the total area of absorbing surface of the jejunum or ileum. Finally, it is probable that faulty absorption of food substances occurs because of a grossly increased intestinal rate.

Among those disturbances interfering with proper food absorption, conditions such as sprue or celiac disease may serve as examples of a physiological abnormality involving the function of the small bowel. Reduction of the area of absorbing surface may be due to a chronic inflammatory process, such as regional enteritis, or to entero-anastomoses which short circuit large portions of the small intestine. Pancreatic fibrosis, with a striking diminution of the digestive enzymes, may cause impaired absorption of foodstuffs because of incomplete or delayed breakdown of proteins, fats and carbohydrates. In each of these conditions, the loss of calorific material is most marked as a result of the failure properly to absorb ingested fats. Steator-

* Presented at the Twenty-ninth Session of the American College of Physicians, San Francisco, April 20, 1948.

From the Department of Medicine, Harvard University, and the Medical Service of the Massachusetts General Hospital, Boston. This work was made possible by the "Fund for Studies in Intestinal Absorption," a grant from the Atlas Powder Company, Wilmington, Delaware.

rhea is one of the striking clinical features to be noted in cases of sprue, pancreatic fibrosis, and following major anastomotic short circuits of the small intestine. Whereas normally the fat content of the stools comprises not more than 4 per cent of ingested fats,[1] under these conditions fecal lipid content may run as high as 40 to 50 per cent of the dietary intake.

Another, as yet unexplained, cause of undernutrition that is of great physiological interest is the operation, subtotal gastrectomy. We have found, as have other observers, that following this procedure an important number of patients remain poorly nourished in spite of an apparently adequate food intake. In this group, one commonly finds an excessive quantity of fat in the stools, which may contain as much as 40 to 45 per cent of ingested lipoid material.[2]

In all of these conditions, nutritional improvement can be obtained with varying degrees of success. Thus in sprue, the use of liver extract or of folic acid in optimal amounts may result in increased intestinal absorption. In this disease, however, the results are variable, and it is rare in so-called nontropical sprue to modify the flat vitamin A tolerance curve so characteristic of this condition. In pancreatic fibrosis, potent pancreatic extracts occasionally may be of great clinical benefit. In patients with a major loss of absorptive surface, secondary to an inflammatory process or to short circuiting operations, overfeeding may be the only therapeutic measure to afford help. In our experience, this has also been true in the treatment of malnutrition secondary to subtotal gastrectomy. Strenuous and prolonged overfeeding imposes real difficulties on both patient and physician, and at times presents an almost insuperable problem.

Because of the underlying deficiencies in fat absorption inherent in the several conditions that have been mentioned, search has been made to determine if other measures can be found which might improve the uptake of fat from the bowel in diseases affecting the function of the small intestine. Certain substances have been developed commercially as emulsifying agents and have been used in industry to effect an even distribution of flavors, perfumes and lipoid substances in an aqueous or lipoid medium. These agents possess emulsifying and "wetting" properties due to their effect on surface tension. Dubos,[3] in 1945, reported the use of one of these agents known as "Tween 60" for the dispersion of tubercle bacilli in an aqueous culture medium. The effect of this substance on the lipoid encapsulated tubercle bacilli was to produce a homogeneous dispersion of the organisms in the culture medium in such a manner that individual colonies could be grown in place of the usual growth in the form of a pellicle. These observations of Dubos suggested the possibility that the use of such an agent, when mixed with food, might provide a more homogeneous and finer emulsification of dietary fats and a better dispersal of lipoid substances when presented to the intestinal mucosa for absorption. We chose the substance polyoxyethylene sorbitan monooleate *

* Sold under the registered Trade Mark "Tween 80" and supplied for this study through the courtesy of the Atlas Powder Company, Wilmington, Delaware.

(hereafter referred to as "PSM") for study of this problem. This preparation is the direct reaction product of sorbitan monooleate with ethylene oxide in the ratio of 20 mols of ethylene oxide per mol of sorbitan monooleate.

Long term feeding experiments by Krantz [4] have shown that no toxic manifestations have followed the feeding of PSM to animals over several generations. In human beings, we have fed as much as 15.0 grams daily for a period of months without any untoward symptoms and without any evidence of toxicity as measured by erythrocyte or white cell changes, liver or renal function tests. In collaboration with the Central Research Laboratory of the Atlas Powder Company we have demonstrated [5] that at least the polyoxyethylene fraction of PSM is excreted quantitatively in the urine and stools. The possibility of oxalic acid poisoning from the polyoxyethylene component would seem, therefore, to be negligible. Furthermore, urinary studies for oxalate content in patients on PSM therapy indicate no increase in oxaluria. The only symptom attributable to the use of this preparation has been the rare manifestation of increased bowel activity.

In order to study the effectiveness of any agent in modifying the absorption of fat from the intestinal tract in human beings, observations obviously may be directed along several lines.

In human subjects on a diet of fixed caloric and fixed fat content, measurements may be made of the daily fat loss in the stools under controlled experimental conditions. Improvements in fat absorption will be reflected in a reduction in fecal fat. Such studies are extremely time-consuming and are possible only on a metabolic ward where diets can be accurately measured and excreta carefully collected. Collection periods must be at least of six or seven days' duration in order to obtain adequate samples, and it is preferable that 12 to 14 day periods be used to obtain conclusive results. Careful and thorough mixing of stools is a difficult procedure but is essential for satisfactory results.

A second method of studying fat absorption, which may be used in an ambulatory patient, is that of following variations in weight over long periods of time, with relative stabilization of activity, dietary intake and therapeutic measures. Conclusions as to the efficacy of a given therapeutic measure under such conditions are of relative value only, but with an intelligent, coöperative patient, valuable studies of this nature may be carried out over intervals of many months.

A third approach to the problem is to attempt to evaluate fat absorption by the oral administration of a fat-soluble substance and the subsequent determination of blood levels of the given substance at regular time intervals. A so-called vitamin A tolerance curve is such a procedure.

We have employed all three measures in attempting to demonstrate the effectiveness of PSM in improving the absorption of fats in human beings.

The first set of observations is shown in figure 1 and represents a composite of vitamin A tolerance curves taken under standard conditions in a

group of 16 normal subjects. Serum vitamin A determinations were made by the method of May et al.[6] on specimens taken fasting and at intervals of three, five and seven hours after the ingestion of 200,000 units of vitamin A ester in fish liver oil. Two weeks after the original control studies were made the tests were repeated, but at this time 2.0 grams of PSM were added to the capsules containing the fatty solution of vitamin A. Figure 1 represents the composite curves obtained in the normal subjects before and after the addition of PSM to the vitamin A test dose. The peak level of vitamin A obtained in the serum is essentially the same in the control curves and following the use of an emulsifying agent. Such a result is probably to be expected, inasmuch as 96 per cent or more of ingested fat is absorbed by nor-

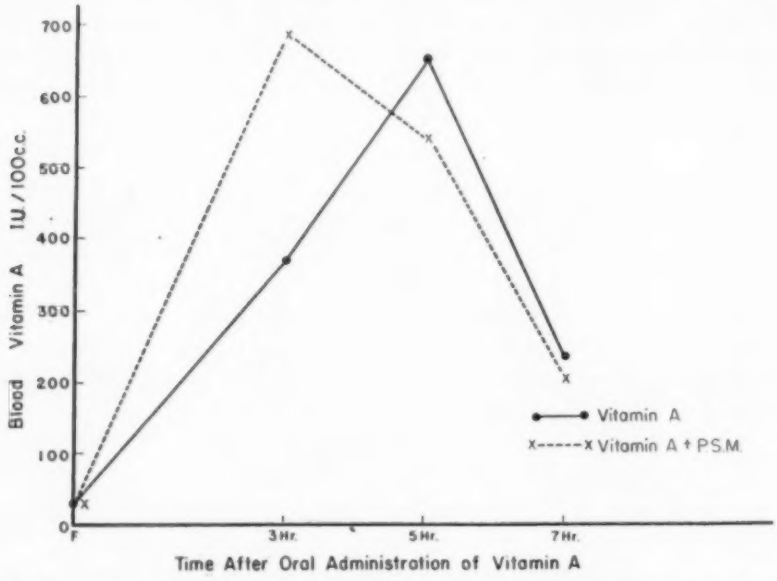

FIG. 1. Composite vitamin A tolerance curves in 16 normal subjects with and without the addition of PSM.

mal individuals. It is apparent, however, that absorption was accelerated after the use of PSM inasmuch as the peak of absorption occurred at about three hours as compared to a peak at five hours in the control studies. In patients suffering from such conditions as subtotal gastrectomy, sprue, pancreatic fibrosis and regional enteritis, similar observations indicate that the addition of PSM to a fatty solution of vitamin A results in important increases in fat absorption. As shown in figure 2, it is evident that in the patients studied, control observations demonstrated a striking interference with fat absorption as shown by low or flat vitamin A tolerance curves. The same patients also gave evidence of their inability to absorb fat normally by the presence of an abnormally high fat content in the stool and by inability to gain weight on ordinary diets. The addition of 2.0 grams of PSM to the test dose of fat-soluble vitamin A resulted in an easily demonstrable increase

in vitamin A absorption, as compared to the original control observations. This increase was outside the error of laboratory technic involved in vitamin A determinations, and in some instances amounted to as much as 400 to 500 per cent of the control peak figures. From these studies, it would seem apparent that the addition of an emulsifying agent (PSM) to a solution of fat-soluble vitamin A accelerated its absorption from the intestinal tract, and in the presence of functional or organic disease of the small bowel, it actually increased the total quantity absorbed.

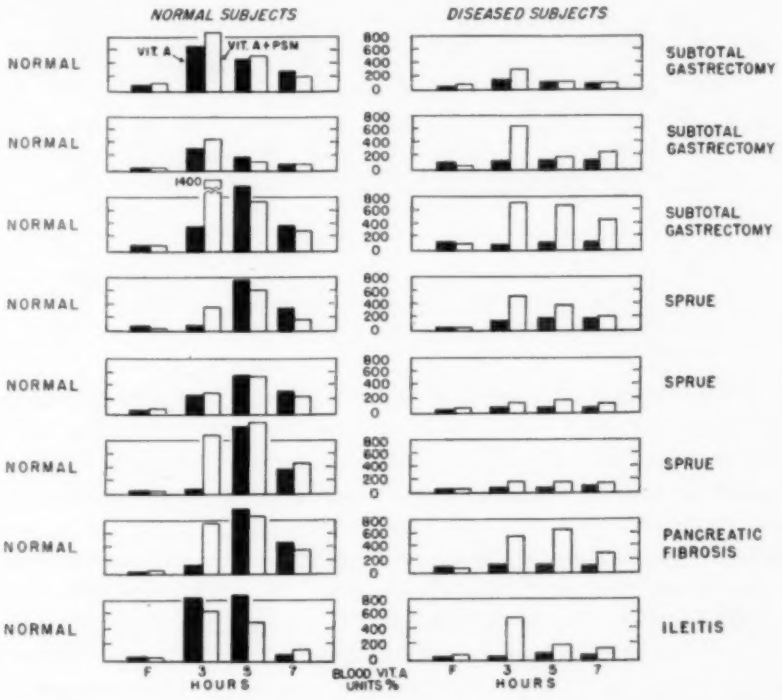

FIG. 2. Comparison of vitamin A tolerance curves in "normal" and "diseased" subjects with oral administration of 200,000 units of vitamin A ester in fish liver oil (black bars) and with 200,000 units of vitamin A ester plus 2.0 grams of PSM (white bars).

In a second set of observations, adequately controlled metabolic studies were made in a group of patients with nutritional difficulties secondary to a subtotal gastrectomy performed for a duodenal ulcer. As already noted, it is not uncommon to find increased quantities of fecal fat after this operation. In a group of four patients, on whom this operation had previously been performed, studies were made on stool fats by the method of Fowweather [7] under control conditions and following the use of various substances that might conceivably increase the absorption of fat from the small bowel. In table 1, it will be noted that no important reduction in the percentage of fecal fat occurred after the use of such substances as desoxycholic acid, folic acid, pancreatic extract, hydrochloric acid, and crude liver extract. In one patient

TABLE I

Effect of Different Supplements on Stool Fats in Patients Showing Malnutrition Following Subtotal Gastrectomy

Case	No. Days Collection Period	Period	Dietary Intake*		Fecal Fat*	
			Fat, Grams	Calories	Grams	% Fat Intake
H. B.	16	Control	107.3	2380	12.6	11.7
	8	Desoxycholic acid 0.3–0.9 gm./day	107.3	2380	14.2	13.2
	24	Folic acid 10–20 mg./day	107.3	2380	15.0	14.0
P. S.	8	Control	119.0	2620	10.3	8.7
	8	Datein 120 gm./day	119.6	2625	10.0	8.4
	24	Datein + pancreatic extract 15 gm./day	139.5	3295	8.0	5.8
S. K.	12	Control	100.8	2200	18.9	18.8
	12	Pancreatic extract 18 gm./day	100.8	2200	22.7	22.4
	6	Pancreatic + essenamine 100 gm./day	109.7	2720	15.8	14.4
B. G.	16	Control	133.1	2395	7.0	5.3
	16	HCl 12 c.c./day	133.1	2395	10.5	7.9
	8	Crude liver extract 2 c.c./day	133.1	2395	10.5	7.8

* Daily average.

(S. K.), the addition of a large amount of a lactalbumin hydrolysate to the diet apparently effected a reduction of some importance in the fat content of the stool. In patient P. S., however, no such reduction occurred when a comparable amount of a similar protein was administered over an eight-day period.

Similar observations on four other patients with subtotal gastrectomies were carried out and are summarized in table 2. All four of these patients were badly nourished and had difficulty in doing more than maintain their weight, even with a very adequate caloric intake. In each instance, the percentage of ingested fat lost in the stool was greater than the generally accepted normal maximum figure of 4 per cent. In the last two cases, the amount of fat lost in the stools was 12.4 and 14.6 per cent of the ingested fat respectively. After adequate control periods on an absolutely constant diet, PSM was added with the meals in doses of 1.5 grams three times a day. In each case, after the addition of this emulsifying agent there was a reduction in fecal fat. In the first two cases, this reduction was moderate but definite. In the last two cases, the amount of fat present in the stools after the administration of PSM was approximately only one-quarter of the amount originally found on a control diet. In patient R. S., the experiment was made of doubling the fat intake after control observations had been carried out. It will be noted that when the daily fat intake had been raised from 98 grams to 183 grams, the percentage of fat lost in the stools remained essentially the same, although the total amount of fat lost was practically double. At this point, PSM was again added to the diet, and its use resulted

TABLE II

Effect of PSM on Stool Fats in Patients Showing Malnutrition Following Subtotal Gastrectomy

Case	No. Days Collection Period	Periods	Dietary Intake*		Fecal Fat*		Gastric Portion Resected
			Fat, Grams	Calories	Grams	% Fat Intake	
E. R.	12	Control	103	2900	11.4	11.0	Upper
	12	PSM	103	2900	9.7	9.4	
R. S.	12	Control	98	2325	6.2	6.3	Lower
	12	PSM	98	2325	3.5	3.6	
	12	Control	183	3095	12.7	6.9	
	12	PSM	183	3095	8.2	4.5	
D. B.	6	Control	100	2800	12.4	12.4	Lower
	6	PSM	84**	2350	3.2	3.8	
J. B.	6	Control	100	2995	14.6	14.6	Lower
	6	PSM	100	2840	3.7	3.7	

* Daily average.
** Patient unable to tolerate such large intake of food as during control period.

in a measurable reduction in stool fats, even though the amounts of dietary fat had been practically doubled.

The findings in Case J. B. are worthy of detailed comment. This patient had an intractable duodenal ulcer, for which elective surgery was indicated. He was admitted to the metabolic ward for control observations prior to operation. The results of these studies are shown in table 3 under "Period I." It will be noted that the percentage of fat lost in the stool during this preoperative control period amounted to 3.2 per cent of 100 grams fat intake. After these observations were made, the patient was operated upon, and a routine subtotal gastrectomy was performed. Twenty-eight days after the operation he was returned to the metabolic ward, and studies were carried out similar to those made before surgical interference. Although the patient

TABLE III

Study of Fat Absorption in a Patient with Duodenal Ulcer. Comparison of Fat Absorption before Subtotal Gastrectomy, 28 Days and 7 Months after Operation, and during Administration of PSM

	Period I	Period II	Period III	Period IV
	Pre-Op. Control	28 Days Post-Op.	7 Mo. Post-Op.- Control	7 Mo. Post-Op. Therapy
Average calorie intake	2400	1460	3000	2840
Fat intake (grams)	100	40	100	100
Total fecal solids (grams)	12.6	21.0	29.0	38.0
Total fecal fat (grams)	3.2	10.8	14.6	3.7
Fat per cent dried wt.	26	26	50	10
Stool fat per cent intake	3.2	27	14.6	3.7
Split fat per cent	58	75	82	18
Weight kg. (normal 75)	60.8	56.4	62.5	62.6
			62.6	63.4

was unable to take an equivalent amount of food, it is of interest to note that with a daily intake of only 40 grams of fat, 10.8 grams or 27 per cent of the ingested fat was lost in the stools. Six months later, after the patient had become reasonably well adjusted to the operative procedure, a third period was run with the patient on a full diet of 3,000 calories containing 100 grams of fat. It will be noted that his weight at this time was only 1.7 kilograms greater than his immediate preoperative weight; it was still approximately 13 kilograms under his normal weight. On the above diet, stool fats amounted to 14.6 per cent of the fat intake. At the end of this period he continued under observation on the metabolic ward with practically no change in his diet, the fat content being constant at 100 grams per day. During Period IV, however, he was given 1.5 grams of the emulsifying agent PSM with each of his three main feedings. In two weeks' time the fecal fat had dropped to a figure almost identical with that observed in the original preoperative control period, or one which is well within normal limits.

It would seem from this set of observations that under conditions such as subtotal gastrectomy, in which the absorption of fat from the small bowel is seriously reduced, we have been able to improve fat absorption by the addition of an emulsifying agent to the diet.

A third type of study was carried out on a young woman of 28 years with a diagnosis of sprue, who was followed as an ambulatory patient for a period of a year and a half. The diagnosis was substantiated by the presence of steatorrhea, postprandial abdominal distention, loss of weight, glossitis, and anemia. Laboratory studies showed excessive amounts of fat in the stools and an absolutely flat vitamin A tolerance curve. For a period of nine months her treatment consisted of a regulated diet, limitation of physical activity, and the administration of folic acid. Her diet contained approximately 2400 calories, consisting of 215 grams of carbohydrate, 90 grams of protein, and 130 grams of fat. Folic acid was administered in daily doses of 15 mg. by mouth and was used because the patient was sensitive to any liver extract. Doses of folic acid larger than 15 mg. a day could not be used because of the appearance of headaches, dizzy spells and loss of appetite. On this regimen, the clinical symptoms of the disease were partially controlled, but over the entire nine months' period there was essentially no gain in weight. As will be seen in figure 3, during the first nine months several determinations of stool fat showed a loss in fecal lipids of approximately 22 grams per day, a very excessive fat loss. At the end of nine months, a single addition to therapy was made, namely, the administration of 1.5 grams of PSM with each of the three meals. Actually, the caloric intake was maintained at a slightly lower level, but the fat content was kept at approximately the same level. Folic acid was continued in the same dosage until the last two months, at which time it was discontinued. During this second period of nine months, there was a slow, steady gain of 21

pounds in weight, and there was no diminution in weight gain after the omission of folic acid. The clinical symptoms during this period were almost completely controlled. It is of interest to note that the steady gain in weight was accompanied by progressive diminution of the amount of fat lost in the stools. The final determination of fecal fat loss was approximately 7 grams per day.

Although this therapeutic experiment is subject to the criticism of not being as completely controlled as were those observations made on the metabolic ward, the patient carried out her regimen faithfully and no important modifications of her dietary or medicinal regime occurred. There can be little doubt that the addition of an emulsifying agent to the diet accompanied and probably caused a progressive gain in weight, and at the

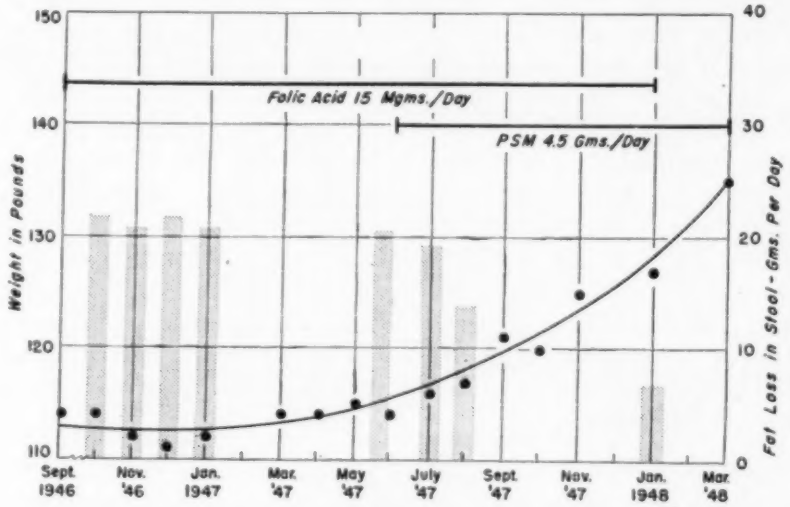

FIG. 3. Weight curve of a patient with nontropical sprue during two 9-month periods; the first on fixed dietary and folic acid therapy only, and the second on the same regimen with the single addition of 4.5 grams of PSM per day. The average fecal fat loss in grams per day at various intervals throughout the period of study is shown by the vertical bars.

same time reduced the fat lost in the stools. It is important to note that in spite of clinical improvement, at the end of this period the patient's vitamin A tolerance curve remained absolutely flat, indicating that the fundamental disturbance of physiology in the small bowel had been unaltered. It is of incidental interest that in this patient with sprue, the addition of PSM to a vitamin A load test changed the tolerance curve from a flat curve to one indicating greater absorption, although it did not rise to normal levels.

DISCUSSION

From the foregoing experimental and clinical observations, we believe that it has been possible to demonstrate in human beings increased absorption of fat and fat-soluble substances by the addition of an emulsifying agent to

the diet. Although the exact mechanism of action is not known, it is probable that the agent, polyoxyethylene sorbitan monooleate, accomplishes this result because of its ability to lower surface tension. The effect primarily is that of a substance capable of modifying opposing interfaces, with resulting improvement of emulsification, "wetting," spreading or dispersion. Such an agent, by lowering surface tension in the case of dietary fats, undoubtedly increases the total surface area of lipoid material to be presented to the intestinal villi by reducing the size of the fat globules. The use of such an agent would seem to represent a new approach to a rather common and difficult therapeutic problem, namely, the control of steatorrhea. In the past, preparations of bile salts have been used with indifferent success in achieving such a therapeutic result. Our studies would lead us to believe that an emulsifying agent, such as polyoxyethylene sorbitan monooleate or some other similar agent, may be of real value in effecting an improvement in the absorption of fats or fat-soluble substances from the small bowel in conditions where absorptive difficulties constitute a problem of major clinical importance. Under normal physiological conditions, the absorption of dietary fat from the intestinal tract is so nearly complete that the addition of such an agent to the diet would seem to be of negligible value. Although confirmatory data are not yet available, it is possible that the use of an emulsifying agent may exert an appreciable influence on the absorption of other substances than fat. In conditions of serious malnutrition secondary to such disturbances as celiac disease, sprue, chronic inflammatory diseases of the jejunum or ileum, anastomotic operations of the upper gastrointestinal tract, and the like, the utilization of such a therapeutic measure may promise significant clinical benefit.

BIBLIOGRAPHY

1. Wollaeger, E. E., Comfort, M. W., and Osterberg, A. E.: Total solids, fat and nitrogen in the feces. III. Study of normal persons taking a test diet containing a moderate amount of fat; comparison with results obtained with normal persons taking a test diet containing a large amount of fat, Gastroenterology, 1947, ix, 272.
2. Wollaeger, E. E., Comfort, M. W., and Weir, J. F.: The total solids, fat and nitrogen in the feces. II. Study of persons who had undergone partial gastrectomy with anastomosis of entire cut end of stomach and jejunum (Polya anastomosis), Gastroenterology, 1946, vi, 93.
3. Dubos, R. J.: Rapid and submerged growth of mycobacteria in liquid media, Proc. Soc. Exper. Biol. and Med., 1945, lviii, 361.
4. Krantz, J. C.: Personal communication.
5. Krantz, J. C., Culver, P. J., Jones, C. M., Wilcox, C. S., and Rose, R. S.: Paper in preparation.
6. May, C. D., Blackfan, K. D., McCreary, J. F., and Allen, F. H., Jr.: Clinical studies of vitamin A in infants and children, Am. Jr. Dis. Child., 1940, lix, 1167.
7. Fowweather, F. S.: Determination of amount and composition of fat of feces. I. Investigation of "wet" method and comparison with "dry" method, Brit. Jr. Exper. Path., 1926, vii, 7.

HEART FAILURE: THE RELATION OF SYMPTOMS AND SIGNS TO ITS SEVERITY AND DURATION*

By WILLIAM DOCK, M.D., F.A.C.P., *Brooklyn, New York*

WHEN the estimation of arterial pressure became a routine clinical method, it was at once noted that in cases of congestive heart failure, or cardiac decompensation, arterial pressure often remained abnormally high up to the time of death. Indeed, Sahli noted that in some patients a rise in arterial pressure occurred with the development of failure and that a fall resulted from treatment successfully directed to restoring cardiac compensation.[1] It also was apparent on the most superficial study of elderly patients with heart failure precipitated by Graves' disease that the total volume flow of blood under basal conditions must be considerably greater than normal, for these patients had warm skin and extremities, a bounding pulse, vigorous precordial impulses and loud heart sounds even when edematous and orthopneic.

These facts did not lead the early students of heart disease to question the concept that the condition known as congestive failure was due to failure of the myocardium to meet the demands imposed upon it by the needs of the body for arterial blood. For it is obvious even in cases with increased output and arterial pressure that the load borne by the heart under basal conditions is far less in cases of heart failure than that borne by the normal heart successfully during hours of sustained physical exertion, especially in those many asymptomatic hypertensives who are capable of vigorous and prolonged effort. Cardiacs were found to be incapable of such exertion, and it was assumed that this was due to a decline in the capacity for work in the failing heart.

In the spring of 1947, several of the most experienced investigators, in discussing elevated cardiac output during episodes of failure, urged that the current concept of heart failure was incorrect, for how could an organ be failing if it was doing more work than normal? Such arguments indicate that the whole problem of functional failure must be widely misunderstood, or that the term "failure" as used in medicine requires a definition in a new and stricter sense. The opponents of the old use of "heart failure," as applicable to cases with high basal blood flow or arterial pressure, gave no new definition and merely offered an agnostic attitude toward the problem. This point of view does not lack authority; it was advanced by recognized authorities in cardiac investigation.[2]

In every clinical field, failure of function is assumed to occur more readily under a heavy load than under a basal one, and failure of function leading

* Received for publication November 1, 1947.
From the Department of Medicine, Long Island College of Medicine, Brooklyn, N. Y.

to serious impairment of health often is seen when the organ is performing more work per day than is necessary to maintain life under basal conditions. It is natural to assume, as most physicians have, that the seriousness of the consequences of any degree of organic failure varies with the load imposed by the body's needs under basal conditions and by the stresses imposed by activity.

For example if a chronic nephritic has been on a normal diet, with 75 gm. of protein per day, and has had a urea output of 24 gm. a day with a constant blood urea level of 125 mg. per cent it is quite probable that he has been free of symptoms. A normal person, on such a diet, excretes 24 gm. of urea daily but has a blood urea of only 25 mg. per cent. If the nephritic's diet is altered, or if severe febrile illness sets in, his protein break-down may rise to 250 gm. per day. If he were normal in his renal capacity for excretion, he would then eliminate 80 gm. of urea a day with a blood level of 70 mg. per cent. But the nephritic's blood urea will rise to 300 mg. per cent before excretion reaches 80 gm. per day, and this may well precipitate severe and even fatal manifestations of uremia. Before death occurs urea excretion may be more than twice the normal level per day, but no physician would suggest that renal failure was not present simply because the imposed load, and the work actually accomplished, were greater than normal.

If such a nephritic had been on a rice diet, with liberal intake of salt and water, the urea excretion might have fallen to 4 gm. a day, and the blood urea to 30 mg. per cent. The normal subject, on such a diet, would have a similar low urea output and a blood level of 8 mg. per cent. No one would suggest that this normal subject was in renal failure because, on a very light load, his kidneys excreted only one fifth the "normal" quantity of urea, or that the nephritic had regained normal renal function because his blood urea now was in the "normal range."

The relations of load, work capacity, and evidence of failure are the same in heart failure as in renal failure. A normal man can have a basal output of 4 liters of blood per minute. During vigorous sustained effort output may rise to 20 liters with little or no increase in the size of the roentgen silhouette of the heart. After a month of starvation, output may have fallen to 2 liters per minute and the roentgen silhouette become much smaller. The cardiac, on the other hand, might have the same basal output, and a roentgen silhouette twice as large, and on starvation might have the same fall in output to 2 liters and a decrease in heart volume to about the size of a normal heart in a person leading an active life on a 2500 calorie diet. If the cardiac happens to have Graves' disease, or anemia with a 60 per cent fall in hemoglobin, his basal cardiac output may be 8 to 10 liters per minute. If such a patient is subjected to conditions which would raise the output of the normal heart to 20 liters, severe disability or even death may occur.

Evidently it is not safe to test the functions of failing organs by forcing them to carry loads which are of value in testing the capacity of normal

organs, and it is not possible to test functional capacity merely by determining the work done under basal conditions, or when work has been brought to minimum levels by diet or starvation. The degree of failure is estimated by obtaining data on the conditions under which the organ manages to perform its work. In the case of the kidney the capacity for function can be measured with great precision by comparing the rate of excretion of one of the metabolites with the plasma content of that substance. Thus the Addis urea ratio, the Rehberg creatinine test and the clearances of inulin, thiosulfate, diodrast or para-aminohippurate give an index of the way the kidney is working. In normal subjects it is necessary to give fluid and raise the blood level of the metabolite in order to get constant values, but when urine specific gravity is fixed and blood levels are elevated by renal failure, no such "loading" may be necessary. The blood levels alone give a rough index of capacity, since the rate of creatinine excretion varies little, and on normal diets even urea excretion varies only between 20 and 60 gm. per day. If creatinine is over 2 mg. per cent (twice the normal level), or urea over 100 mg. per cent (three times the usual level), the kidney is not working properly.

In the liver, function can be judged by comparing the blood levels and rates of excretion of bilirubin, bromsulfalein, rose bengal, etc. In the heart and in the hollow viscera, motor function can be judged by the amount of content moved and the volume of the viscus at the end of a phase of active movement. Thus, the volume of gastric content seven or twelve hours after a standard meal, of the urinary bladder at the end of micturition, and of the heart at the end of systole, serve as indices of the capacity for motor function.

Some species of mammals have almost no blood in the ventricular chambers at the end of systole under basal conditions of flow, but in man the heart volume at the end of systole is greater than that of the empty heart. Normally its volume with the ventricular content at the end of systole is 30 to 60 per cent greater than the volume of the myocardium, but with the low cardiac output and blood pressure of acute hemorrhage the volume may be only 5 or 10 per cent greater than if it were completely empty. In heart failure the volume of the ventricles, at the end of systole, may be 300 to 500 per cent greater than the volume of the empty heart. In a normal person increase in cardiac output evoked by rapid intravenous infusion of saline raises the volume of the ventricular content well above the basal figure.

Myocardial efficiency, as Starling proved in animal experiments, can be measured by comparing the ventricular volume with the work per beat, just as renal function is measured by comparing the blood level of a metabolite with its rate of excretion. At normal rates of contraction, the energy liberated and the oxygen required by the heart are proportional to its diastolic volume. In normal subjects accurate estimation of cardiac efficiency can be made only by raising the mechanical work well above the basal level. This can be done safely, when the roentgen silhouette is normal in size under basal

conditions, by massive intravenous infusion of saline. However, once the heart volume under basal conditions is abnormally large, the function of the organ can be evaluated by studies made without additional loads of work; and such test loads as may be imposed in normal subjects may lead to discomfort and danger in those with failing hearts.

In normal subjects the cardiac output and the systolic pressure rise following epinephrine or effort, but the cardiac silhouette may remain unchanged, may increase or decrease in area. Vasodilatation in muscles, increase in rate, and perhaps metabolic effects of the procedure increase the efficiency of systolic contraction so that the stroke volume rises slightly and minute volume increases greatly with minimal change in volume of the heart. Epinephrine and effort may have similar effects in early heart failure, when symptoms at rest occur only on recumbency, and heart volume is but moderately increased. Under these circumstances effort may be well tolerated but intravenous infusion at rapid rate may markedly dilate the heart and precipitate severe pulmonary edema. Hence the loss of function in dilated hearts must be calculated under basal conditions, and not during effort or infusion. By using diodrast angiography to visualize the heart chambers and the catheter to measure cardiac output and pulmonic arterial pressure, the clinical physiologist can obtain all the data necessary to calculate ventricular efficiency, using work and diastolic ventricular volume. This is no more inconvenient to the patient, or arduous for the investigator, than catheterizing a ureter and measuring minute output and blood levels of a metabolite such as creatinine in order to calculate the function of either kidney. Such precise measurements are of value to the physiologist but they have no place in clinical medicine except in laboratories where fundamental problems in clinical science are being studied.

Clinically, failure may be defined as a loss of organic function sufficient to produce symptoms apparent to the patient, or signs apparent to the unaided eyes of a trained observer. The greater the loss of function, the less the load necessary to evoke symptoms or signs. When symptoms or signs are apparent with loads of work less than the minimal level observed in normal subjects, the loss of functional capacity in the heart, liver, kidneys, or pancreatic islets probably is over 90 per cent. Symptoms may occur, if the load is two to five times the normal basal level, when loss of function is more than 50 per cent. A cardiac with beriberi or Graves' disease, who is not entirely comfortable at rest and recumbent, has probably suffered a decrease of about 80 per cent in cardiac function, and is in heart failure with an output twice normal.

The heart, liver and kidney may fail because of intrinsic disease, or because the flow of blood into the organ is insufficient. Here we refer not to the blood which nourishes and supports the organ, but the blood on which it performs a mechanical or metabolic function. In the case of the liver, diversion of the portal flow may raise oxygen tension in the organ while

reducing its functional capacity. In the heart the flow of blood into the chambers is independent of that to the muscle, and failure of the circulation may occur if high pericardial tension, low pressure in the venae cavae or shortening of diastole due to excessive rise in rate (paroxysmal tachycardias over 200 per min.) prevent normal diastolic filling. It is best to describe such a state as circulatory failure due to shock, hemorrhage, tachycardia, tamponade, constrictive pericarditis, or whatever, so as not to confuse it with congestive heart failure due to loss of myocardial function. In the kidney, vasoconstriction and decline in cortical metabolism set in early in shock or hemorrhage, so that renal function may decrease and blood urea rise in the absence of organic renal disease or serious circulatory defect in other vital organs. This, then, should be called circulatory renal failure.

In the healthy young adult, with no myocarditis, the myocardium can sustain for long periods the labors imposed by valve lesions, high basal rates of flow, hypertension and a vigorous way of life. Often this is possible with no increase in heart volume. On the other hand, the aging heart may dilate and fail even though the patient is sedentary, the blood pressure and cardiac output at low normal levels. Between these extremes of compensation and decompensation is the great range of patients with varying degrees of overloading and of loss of function of the ventricular muscle. In the management of each case, the variations in heart volume, in symptoms and in signs, from time to time and in relation to therapy and activity, are of far more importance than precise measurement of ventricular efficiency on any one date.

McMichael and his co-workers have clearly defined the significant differences, in etiology, prognosis and therapy between failure associated with low or normal basal levels of cardiac output, and that associated with high output.[3] The former can be recognized clinically by the coolness of the extremities and skin, and by a low pulse pressure in the absence of murmurs of aortic valve disease. Since pulse pressure, at any given stroke volume, rises with the diastolic pressure, hypertensive patients have a relative, and not an absolute, decrease in pulse pressure.

But increase in cardiac output is not the only cause of increased load on the ventricles, even if it is the most significant one in precipitating failure. The level of the systemic arterial pressure must be considered in its relation to left ventricular failure, the loud pulmonic second sound present in pulmonic hypertension must be considered in cases of right ventricular failure, and murmurs diagnostic of valvular stenosis or incompetence, or of arteriovenous shunts must be borne in mind when estimating whether overloading under basal conditions is present even though the cardiac output is normal or less than normal. These are the factors which, with the heart volume seen by roentgen-ray and the signs and symptoms of failure, are used to evaluate the relative degrees of myocardial failure and of overloading which are present.

Because heart failure is primarily an example of muscular fatigue associated with incomplete recovery of the ventricle in diastole, any increase in rate of beat or shortening of diastole diminishes the capacity for work by the myocardium. Even in young people, prolonged tachycardia, with normal or reduced arterial pressure and minute volume flow of blood, leads to dilatation of the heart; in older ones failure is often precipitated by rise in rate due to arrhythmia. Disturbances of intraventricular conduction, which prolong systole and shorten diastole, also predispose the heart to fail even though work per beat and rate per minute remain normal. Therefore, the clinician evaluates the state of the myocardium from the apparent degree of failure and the rate of beat. The slower the rate and the more normal the duration of the QRS complex of the electrocardiogram, the more severe must be the damage to the myocardium to precipitate failure of any given type and severity. If the rate is rapid, and the QRS, because of injury to the Purkinje fibers, is over 0.14 second, failure may occur which completely clears up at normal rates and with normal conduction time, thus proving the anatomic and enzymatic integrity of the myocardium.

In heart failure systole is prolonged.[4] When the QRS is not over 0.08 second in duration, increase in the quotient given by dividing duration of systole by the duration of the cycle is regularly associated with other evidence of failure. An altered form of the ballistocardiogram also results from failure and prolongation of systole. Gallop rhythm, bizarre ballistocardiograms, and prolonged systole, if encountered in patients with normal duration of QRS, serve as objective proof that the myocardium is inflamed, fibrosed, or suffering from some metabolic dysfunction. The functional capacity has been reduced, and usually some degree of dilatation is present in such instances.

So far nothing has been said concerning venous pressure or circulation time. Venous pressure in the neck can be judged by inspection as the patient is shifted from recumbent to sitting and the level of venous engorgement above the heart is observed. Direct measurement can be made from an arm vein or with the catheter in the right auricle. The pressure depends on the degree of cardiac failure and on the load imposed on the heart, as well as on the average level of intrathoracic pressure. When respiration changes from gasping to grunting the intrathoracic pressure, and with it the venous pressure, rise 3 to 8 cm. of water, and the cardiac output falls. The observed pressure must be correlated with the type of respiration, degree of emphysema, pulse pressure and coldness of the finger tips to permit an estimation of cardiac output in relation to right auricular pressure.

Circulation time depends on volume of the heart chambers, on degree of venous engorgement, and on the minute volume flow.[5] The velocity of flow may be relatively high, arm-to-lung or arm-to-tongue time relatively brief, in patients with high output failure (beriberi, Graves' disease, high fever, severe anemia, arteriovenous fistulae, Paget's disease of bone, etc.). Neither

venous pressure nor circulation time is an accurate index of myocardial efficiency.

The relation of venous pressure to heart failure has been misunderstood and there has been confusion about the relation of venous pressure to edema. In mitral stenosis it is usually, and we think correctly, assumed that the rise in pulmonic arterial pressure is secondary to a rise in pulmonic venous pressure. The arterial pressure in these cases has been measured by the catheter method and found to be 60 to 120 mm. Hg, the normal 15 to 30. One who ascribed edema solely to high venous pressure would scarcely believe that no clinical evidence of pulmonary edema and no hydrothorax might be found in many such patients, but this is a well-known clinical fact. Even after right heart failure has set in and the liver is enlarged, the lungs of a mitral stenosis case may be free of râles. No one doubts that high venous pressure is, and for years has been present in the lungs of such patients, or that pulmonary edema can develop rapidly in certain types of acute left ventricular failure. Edema usually does not develop when venous pressure rises gradually, as in the lungs with mitral stenosis or in the legs and ankles of young people when they grow up and the column of blood between the ankles and the heart reaches a height of 100 cm. or more. Whether this freedom from edema is due solely to vascular thickening with rise in pressure, or is aided by increased flow of lymph, has not been determined. It is important to recognize that edema may be entirely absent in severe chronic venous hypertension, but occurs readily with acute episodes of moderate rise in venous pressure. Rate of change in conditions, rather than degree of change, often explains the severity of symptoms in many types of organic failure. Rate of development of failure often explains not merely severity, but the actual character of the symptoms.

Unless the kidneys fail suddenly and completely (i.e. acute anuria or oliguria) there will be no symptom due to "forward" failure of urine flow. In the chronic disorders anuria is only an agonal event. This is also true in the heart; symptoms similar to those of shock only occur when the heart is suddenly and very severely injured, or its filling suddenly impaired by tachycardia or by tamponade. Then a weak or impalpable pulse may result, and weakness, sweating, loss of consciousness, anuria and paralytic ileus may occur. Except with myocardial infarct or massive pulmonary embolism actual myocardial failure rarely develops suddenly. Even when these accidents precipitate acute failure with symptoms of shock ("forward failure"), if the patient survives a few hours compensatory changes set in and the usual signs of congestive failure—rise in venous pressure, pulmonary edema, hepatic swelling and tenderness—appear.

The first evidence of these compensatory changes is a rise in systemic venous pressure, in cases of pulmonary embolism, and the development of râles in the caudal, dorsal lung fields in myocardial infarction or rupture of an aortic or mitral leaflet. In vigorous young men the normal blood volume

is relatively large and these signs may develop rapidly even when the sudden injury produced few or no symptoms of shock or "forward failure." In elderly sedentary patients this rarely occurs, because, with average levels of blood volume the rise in venous pressure due to sudden heart failure, with the output of one ventricle markedly embarrassed, is not sufficient to produce symptoms and signs in the first few minutes, or even in the first few hours. Such clinical observations confirm Welch's classic studies on the difficulty of producing acute pulmonary edema in dogs by clamping off the aorta or a large part of the left ventricle. High venous pressures are due not to "backward failure" but to the physiologic responses to a reduction in blood flow below the optimal level in all the tissues of the body. This is why congestive failure, in its most advanced form, can be seen in patients whose basal cardiac outputs are well above normal, but insufficient to meet the abnormal tissue needs created by anemia, lack of thiamine, or excess of thyroglobulin, or the abnormal circulatory conditions due to arteriovenous shunts. Those who have likened "backward failure" to the condition in Harvey's celebrated experiment, in which the snake's aorta was ligated and its venae cavae became tense and swollen, have ignored the fact that congestive heart failure often is severe even though the heart is moving more blood per minute than it does in normal resting subjects. The anasarca, the high venous pressure, the greatly increased volume of plasma and red cells in the body—in a word, all the characteristic features of chronic heart failure—are due, not to the heart's damming back blood, but to a discrepancy between the optimal flow to the tissues, and the flow provided by the failing myocardium.

In acute failure this discrepancy may be severe enough to produce syncope without causing pulmonary edema; in chronic failure it causes all the changes just noted, even though no fall in arterial pressure and no decrease in blood flow to the brain and heart have resulted. The earliest response to a decrease in cardiac output is a rise in venomotor and vasomotor tone, which restores arterial pressure and helps to maintain cardiac filling. But only in vigorous young people, whose blood volumes are relatively high from constant strenuous activity, is the resulting shift of blood from the periphery to the great veins and the thorax sufficient to cause an immediate distention of neck veins or pulmonary edema as a result of acute heart failure.

When decrease in cardiac output is due to shock or hemorrhage, the immediate effect of changes in the tone of venules and arterioles is to bring venous pressure back toward normal, and to shift the balance of fluid exchange between blood and tissues toward the intravascular side. Thus, blood volume tends to increase by hemodilution, unless the patient is dehydrated. In acute cardiac failure, with a rising venous pressure, increase in blood volume occurs more slowly, and it is only after days or weeks of failure that the blood volume rises to levels sufficient to cause intense engorgement of the viscera and the great veins. This rise in blood volume, and therefore all the usual manifestations of congestive failure, are thus sequelae of a low

cardiac output, just as is the replacement of blood volume after a donation to a blood bank. Sodium retention and fluid retention are effected through changes in activity of the hypothalamic, and hypophyseal-adrenal cortical mechanisms. They are facilitated by the decrease in renal blood flow which is the first response to reduced cardiac output. These changes in renal blood flow, in sodium excretion and in blood volume all occur in normal subjects kept in the upright position, which in itself reduces cardiac output by trapping blood in the distended veins below the diaphragm and thus reducing cardiac filling.[6] Increase in blood volume may also be mediated through the nervous system, since polycythemia has been observed with cerebellar tumors, or this may be due to vasoconstriction in vessels supplying the liver and the bone marrow. Whatever the mechanisms involved, red cell and plasma volume atrophy in heart failure just as they do after hemorrhage. Retention of salt and water lead to edema, which is most apparent in the sites where tissue pressures and pulse pressure are low and venous pressure high.

It is now apparent that the rise in arterial pressure in heart failure, first noted by Sahli, and all the classical features of congestive failure are due to the fact that mammals have developed a complex and effective mechanism for dealing with the decrease in cardiac output occurring in shock, hemorrhage and dehydration, and that this mechanism comes into play whenever the cardiac output is reduced for any reason whatever. Without such a mechanism heart failure would result only in fatigability, or if severe, in anuria, abdominal distention, weakness and syncope. The mammal evolved no reflex mechanism for dealing with myocardial failure as such, for the obvious reason that wild animals do not have heart failure during the normal reproductive life span. In civilized man the development of congestive failure is hastened by the high salt content of the diet, which makes possible rapid increases in blood and intercellular fluid volume, and by alternation between an erect posture, which diminishes cardiac output, and recumbency, which allows blood and edema fluid in the legs to be mobilized and pile up in the lungs.

All of the classical symptoms of congestive heart failure can be relieved by bleeding and by use of mercurial diuretics and salt restriction, which deplete the extra-cellular fluid reservoir and eventually lower blood volume and venous pressure. In some cases these symptoms can be relieved by trapping blood in the limbs by tourniquets or cuffs under suitable tension. Digitalis, which increases myocardial efficiency, also diminishes the venous return. If the heart has been filled at auricular pressures above the optimal, all these procedures, as McMichael has shown, may increase rather than diminish cardiac output. However, in high output failure, symptoms are marked before myocardial inefficiency has reached a point at which rise in venous pressure reduces cardiac output. In such cases, this type of treatment will lower cardiac output. Should the output fall critically as a result of bleeding

or digitalization, syncope, extreme weakness and death may occur even though venous pressure is still abnormally high, and cardiac output higher than in a case of low output failure prior to effective therapy. For when metabolic, hemic, or shunt-like vascular defects raise the need for minute volume flow for the whole body, a reduction in venous filling can not be compensated and a shock-like condition sets in. The brain and heart, robbed by the increased flow to other tissues, may then be irrevocably damaged as the cardiac output falls to or below the normal basal minute volume.

Summary

The term "heart failure" should be applied only to the clinical disorder which is due to inability of the myocardium of the ventricles to maintain the *requisite* flow of blood to all the tissues of the body. "Circulatory failure" should be used for those conditions in which requisite flow is not maintained, in spite of an adequate myocardium, because shock, hemorrhage, pericardial tamponade, constrictive pericarditis, or extreme rates of tachycardia prevent adequate diastolic filling of the ventricles. Both heart failure and circulatory failure can be acute (minutes or hours), subacute (days) or chronic (weeks to decades). Shock and hemorrhage produce only the acute form. In acute failure, whether myocardial or circulatory, the pulse is diminished, blood pressure may fall, and weakness, syncope or anuria may follow. In the chronic form of either type of failure, there are rarely any of these phenomena, but instead venous distention and congestion of the lungs or liver dominate the clinical picture.

In heart failure the basal cardiac output of blood, the pressure in the pulmonic artery or the aorta, or the work of one ventricle in cases of an insufficient valve, may be above normal almost until death. The measure of the loss of efficiency of a ventricle is given by the decrease in the quotient of the formula: ventricular work divided by diastolic ventricular volume. Clinical estimation of the loss of efficiency can be made from the signs of increased cardiac work and from the heart size as seen under the fluoroscope. The signs and symptoms of congestion in the lesser and greater circulation are secondary to failure of the heart to supply the tissues adequately with blood. They provide an index of the severity and duration of failure of the tissues to be adequately perfused, but can not be interpreted as measures of, or even evidence for, myocardial failure.

The basal cardiac output is not necessarily reduced in myocardial failure, and in many cases the increase in cardiac output which is present has precipitated heart failure with a relatively high level of cardiac efficiency, just as a high protein intake precipitates uremia with relatively competent kidneys.

BIBLIOGRAPHY

1. Sahli, H.: Herzmittel und Vasomotormittel, Verhandl. deutsch. Kong. f. inn. Med., 1901, xix, 45–54.
2. Burwell, S., and Dexter, L.: Cardiac output in a case of beriberi, Trans. Assoc. Am. Phys., 1947, lx, 59–64.
3. McMichael, J.: Circulatory failure studied by means of venous catheterization. Advances in Internal Medicine, Interscience Publishers, New York, 1947, ii, 60–101.
4. Taran, L. M., and Szilagyi, M.: Duration of electrical systole in acute rheumatic carditis in children, Am. Heart Jr., 1947, xxxiii, 14–26.
5. Nathanson, M. A., and Elek, S. R.: The influence of heart size on circulation time, Am. Heart Jr., 1947, xxxiii, 464–476.
6. Brun, C., Knudsen, E. O. E., and Raaschou, F.: Kidney function and circulatory collapse, Jr. Clin. Invest., 1947, xxv, 568–574.

THE SHOULDER–HAND SYNDROME IN REFLEX DYSTROPHY OF THE UPPER EXTREMITY *

By Otto Steinbrocker, M.D., *New York, N. Y.*, Norman Spitzer, M.D., *Yonkers, N. Y.*, and H. Harold Friedman, M.D., *Denver, Colorado*

A variety of seemingly unrelated clinical disorders, usually considered distinct entities, have been described in the surgical and medical literature for many years. These conditions include causalgia,[1, 2, 3] Sudeck's atrophy (post-traumatic osteoporosis),[4–12] painful disability of the shoulder following coronary occlusion,[13–19] post-infarctional sclerodactylia,[20] palmar and digital contractures as well as Dupuytren's contracture,[21–26] the swollen atrophic hand associated with cervical osteoarthritis,[37] certain changes in the paretic limbs of hemiplegics,[27–32] and a number of others. In this group belongs the idiopathic shoulder-hand syndrome.[33] It is becoming increasingly apparent that, although the etiology of these various syndromes may be different, many of their clinical features, and probably the neurovascular mechanisms underlying their development, are very similar, if not identical.[34, 35]

Certain clinical features common to these disorders have been termed reflex dystrophy by de Takats.[13–16] This designation refers chiefly to the characteristic vasomotor and trophic disturbances in the affected extremity provoked by an etiologic factor through neurovascular reactions. The vasomotor and trophic symptoms usually are presumed to arise from reflex stimulation of the sympathetic nerve supply. Some authors, accordingly, add "sympathetic" to the term as in "reflex sympathetic dystrophy." The interpretation of the underlying mechanism in these diseases largely represents a clinical presumption supported by an abundance of empirical material. Even with the present incomplete knowledge of these disorders the use of the term "reflex dystrophy" is warranted as a working basis.

The most recently described clinical picture which must be regarded as a form of reflex dystrophy is the shoulder-hand syndrome, particularly the idiopathic variety, reported by one of us (O. S.).[33] This condition consists of a peculiar combination of painful shoulder disability with homolateral pain and swelling of the hand described in six otherwise healthy adults, seen over a period of nine years.[33] In five of the patients the swelling of the hand was followed by trophic changes. Owing to the absence of any history or evidence of preceding trauma or associated disease these cases were presented as the "idiopathic" manifestation of the disorder. The clinical picture and course in the idiopathic variety resemble those produced by the different etiologies to be considered later [33] (figure 6). The recognition of this com-

* Received for publication October 8, 1947.
From the Arthritis Clinic and Medical Service, Fourth Medical Division (New York University), Bellevue Hospital.
Aided by a grant from the Robert Trubek Rheumatism Fund.

bination of shoulder and hand symptoms as the expression of the same disorder, whatever its origin, rather than as a coincidental involvement of the shoulder and hand by unrelated causes must be stressed.

TABLE I

Reflex Dystrophy of the Upper Extremity

Clinical Forms
- A. Incomplete (Abortive)
  1. Contractures of the palmar fascia and Dupuytren-like contracture.
  2. Painful vasospasm or vasodilatation of the hand.
  3. Swelling and atrophy of the hand.
  4. Painful disability of the shoulder.
- B. Complete
  1. The shoulder-hand syndrome.

The present report is based on a study of 42 cases of reflex dystrophy of the upper extremity followed for periods of one month to nine and one-half years. Thirty-six of these patients presented the shoulder-hand syndrome due to a variety of causes or associated factors shown in table 2.

TABLE II

Etiologic Varieties of Reflex Dystrophy of the Upper Extremity (the Shoulder-Hand Syndrome) in Our Series

- A. Idiopathic
- B. Peripheral Lesions
  1. Trauma and suppuration of the extremity (Sudeck's atrophy, causalgia, post-traumatic osteoporosis, acute bone atrophy).
  2. Vascular disease (thrombophlebitis, diffuse vasculitis, periarteritis nodosa).
  3. Intraforaminal osteoarthritis of the cervical spine (Oppenheimer).
  4. Cardiac disease—post-infarctional.
  5. Other thoracic diseases (post-pneumonic, etc.).
  6. Nodular panniculitis (Weber-Christian).
- C. Lesions of Cord and Ganglia
  1. Herpes zoster.
  2. Diffuse vasculitis?
- D. Higher Lesions
  1. Cerebral lesions (hemiplegia).

From our studies and a survey of the literature it seems plain that reflex neurovascular dystrophy may be provoked by many agencies, but the variations in its manifestations have led to some confusion perpetuated by the multiplicity of its clinical descriptions and designations. It may be useful, therefore, to coördinate the many closely related conditions obviously belonging in this category and differing chiefly in etiology or in minor clinical details.

The subject may be further clarified by regarding the variable clinical features as expressions of the different degrees of reflex neurovascular and motor response to provocative internal or external agents. Although the most extensive clinical picture of reflex dystrophy of the upper extremity is embodied in the shoulder-hand syndrome, certain characteristic signs may be absent in some cases. We have found too that, during its development in some patients, reflex dystrophy evidently may be arrested by treatment, with or without residual changes. It may undergo spontaneous partial or

complete resolution, however, at any stage, again with or without persistent alterations. We have come to recognize, therefore, certain incomplete or abortive forms to be described, as well as its typical, most severe evolution as the shoulder-hand syndrome as listed in table 1.

Reflex neurovascular phenomena usually arise as a complication of some primary condition. In many of these instances the superimposed reflex disorder, by the severity of its symptoms or its inevitable and disabling progression, may rapidly overshadow the underlying cause in diagnostic and therapeutic importance.

Reflex dystrophy occurs in the face, lower extremities and spine, but we are concerned here only with its development in the upper extremity.[4, 34]

Why "the Shoulder-Hand Syndrome"?

The need for segregating one pattern of reflex neurovascular dystrophy as a special entity deserves some consideration. The upper extremity is provided with a relatively rich network of sympathetic communications. There is a more or less indirect but intimate relationship between the thoracic viscera and the upper limbs, the brain and the musculoskeletal structures of the upper part of the body, mediated through the abundant autonomic nerves and ganglia of the cervico-thoracic area. Disease in these parts appears to express itself more frequently than is appreciated by reflex neurovascular symptoms in the upper limb.

For some reason we have not observed, so far, any set of reflex phenomena in the lower extremities analogous to the shoulder-hand syndrome. Moreover, the lack of previous correlation of the shoulder and hand involvement as signs of the same disorder in the cases seen by us, as well as in the most recent literature, seems to require the use of a term which crystallizes the chief features of the condition.

The emphasis on the unity of the shoulder and hand symptoms conferred by a special term may stimulate more frequent and earlier diagnosis as well as more rational, less strenuous therapeutic measures than have been reported even in the latest studies.

Clinical Course of the Shoulder-Hand Syndrome

Diagnosis of the shoulder-hand syndrome can be facilitated by a clear-cut understanding of the usual progress of this disorder. It passes through several stages in each of which the signs resemble different diseases. The syndrome may be divided roughly but conveniently into three stages, or phases, according to the observations made on our patients.[8] Sometimes overlapping of symptoms is observed in the various stages, and the duration of these phases may vary somewhat from the time intervals stated.

The *first stage* (figures 1, 6), which usually lasts three to six months, consists ordinarily of the appearance of painful shoulder disability followed by swelling, pain and stiffness of the hand and fingers. The onset may be

gradual or sudden. Complaints may arise first either at the hand or shoulder followed by symptoms at the other location, or both parts may be affected simultaneously. Pain and limitation of motion develop at the shoulder girdle with diffuse tenderness there, very much as in periarthritis or bursitis. The swelling of the hand and fingers is uniformly distributed and, as a rule, yields little or no pitting to pressure, although in acute onsets

FIG. 1. Phase 1. Painful disability of left shoulder five months, swelling of left hand nine weeks.

striking pitting may be encountered at times. The skin of the hand and fingers becomes smooth and taut, so that the normal wrinkles and creases become shallow or obliterated. Degeneration and desquamation of the superficial layers of the cutis, to a lesser degree on the forearms, occurred

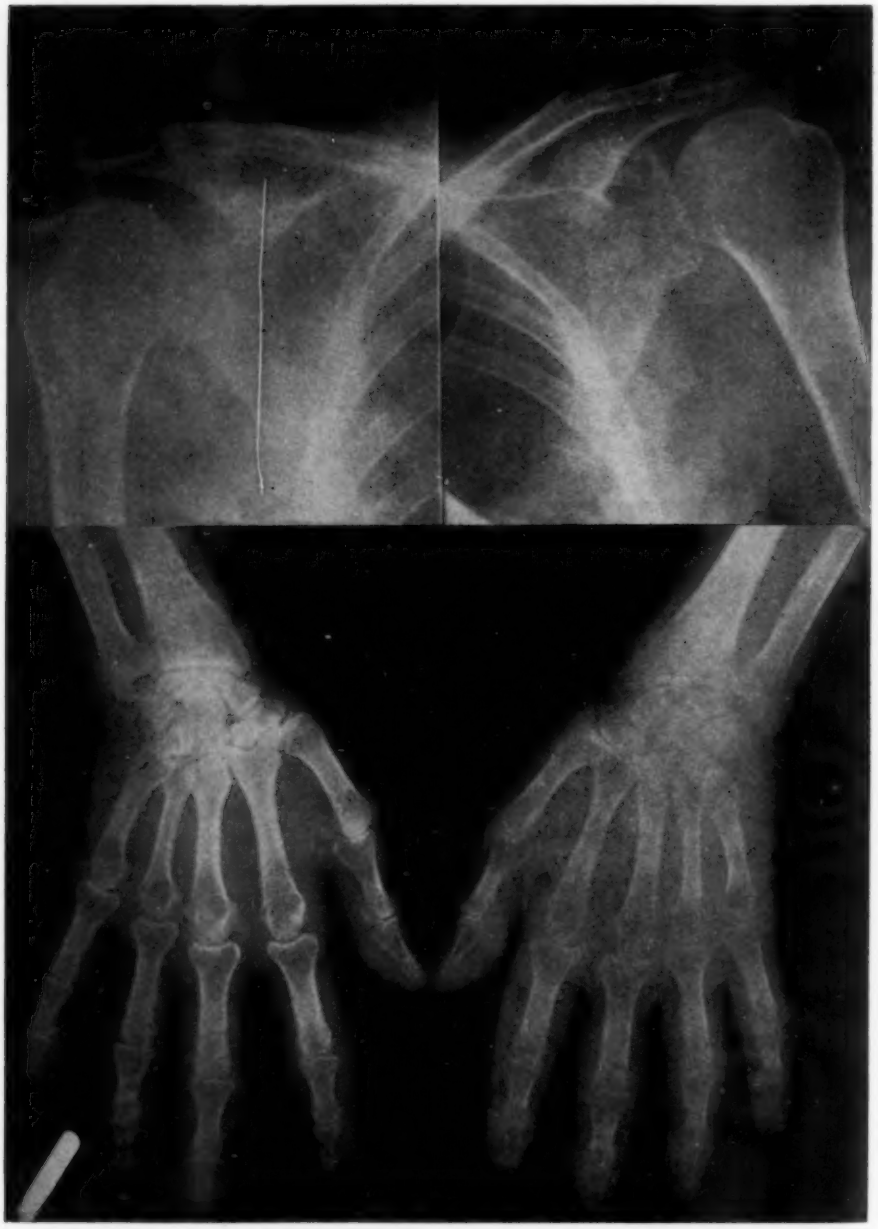

FIG. 2. Typical osteoporosis, wrist and small joints of patient in figure 1. Some decalcification of left humeral head.

in two instances. The color of the affected hand is apt to be a dusky pink or red at first. Later, the swollen tissues become pale or even cyanotic. Limited mobility at the finger joints is noticed. Attempts at passive motion at these articulations often induce pain. The patient usually holds the hand and fingers in a position of slight flexion. The grip is weak.

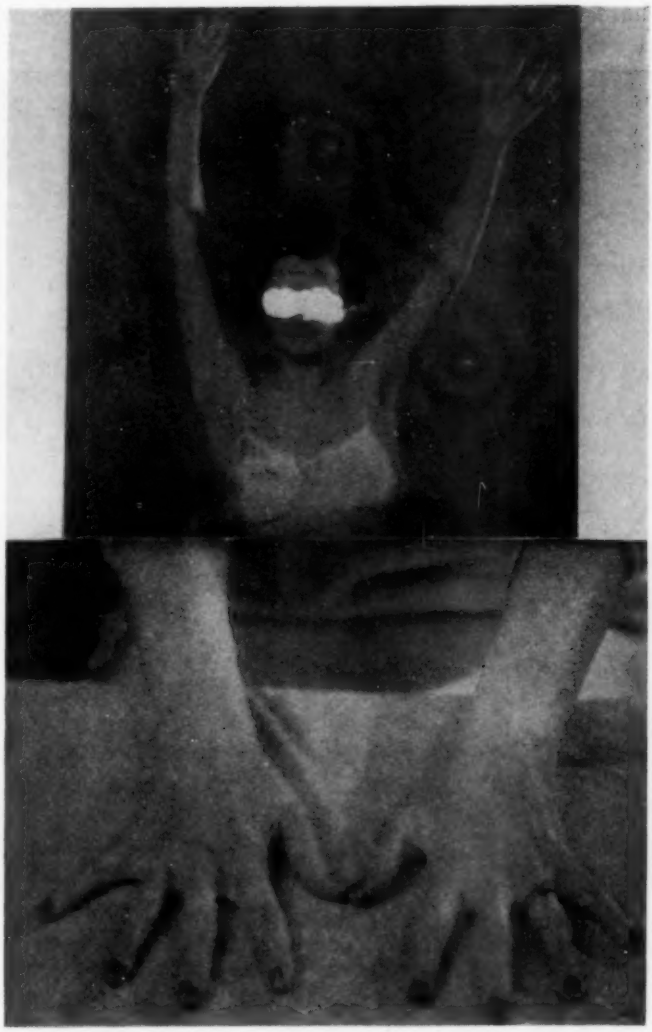

FIG. 3. Successful treatment; recovery about one year from onset (patient in figure 1).

The cutaneous temperature of the limb, especially of the hand, is elevated. The blood flow to the extremity, as reported in plethysmographic and oscillometric studies,[5-8] is likely to be increased. Venograms done by us have shown a suggestive but not, as yet, diagnostic pattern. Hyperreflexia may

be elicited in the affected extremity. At this stage roentgenograms of the hand usually exhibit slight, if any, osteoporosis, excepting in traumatic disorders when the decalcification, mottled or "ground-glass" appearance, of the wrist or even of the whole hand or extremity may develop with astonishing rapidity (figure 2).

The *second stage* (figure 4), which likewise is apt to last three to six months, is characterized by gradual relief of the painful shoulder dysfunction

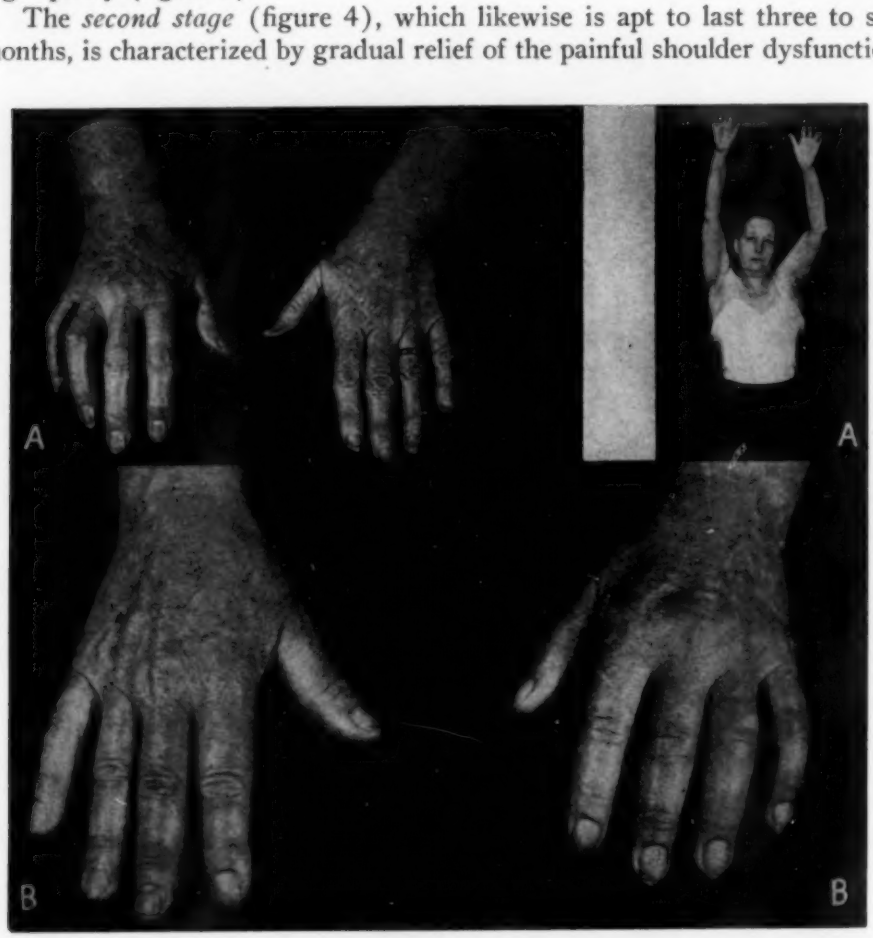

FIG. 4. Phase 2. In 4*a* residual disability at shoulder still present. Swelling of hand resolved in both cases; note smoothing of skin folds on dorsum of fingers; shiny, atrophic skin and digits; in 4*b* beginning flexion contracture more marked.

and resolution of the swelling of the hand. As the swelling subsides, the stiffness and flexion deformity of the fingers become more pronounced in cases with progression. Atrophy of the subcutaneous tissue and intrinsic muscles of the hand may now begin to become apparent. Rolling up of localized areas of the palmar fascia may be noticeable, or early signs of a Dupuytren-like contracture with or without its cutaneous callus may appear. Early trophic changes in the skin are observed for the first time. Reaction

of degeneration in the affected extremity was reported in some of his patients by Oppenheimer.[37] Patchy osteoporosis of the bones of the hand becomes more striking in the roentgen-ray films. The cutaneous temperature, previously elevated, begins to fall. The blood flow to the limb diminishes.[5-8]

The *third stage* (figures 5, 7), which lasts months or goes on to irreversible alterations, is characterized by the marked progression of trophic changes in the hand. The skin becomes smooth, glossy and drawn, with great diminution in the number of creases and wrinkles. Atrophy of the subcutaneous tissue advances. With the developing trophic alterations of the skin there is frequently seen a hypertrichosis, particularly noticeable on the dorsal surface of the fingers. The blood flow to the extremity is diminished and the cutaneous temperature drops, especially over the hand and fingers. Oscillometric readings at the wrist may be lowered. The hand shows great atrophy of the interosseous muscles with severe limitation of motion at the metacarpophalangeal and interphalangeal joints. Contractures of the flexor tendons occur often at this stage, particularly on the ulnar side (figure 7). Subluxations are present occasionally. Rolling up of the palmar and digital fascia, in many ways like Dupuytren's contracture, is common. The roentgenograms at first show spotty decalcification of the small bones of the hand and of the metaphyses of the long bones. Osteoporosis of the humeral head often occurs when shoulder disability is prolonged (figure 2). Later this bone atrophy may become very widespread and diffuse.

FIG. 5. Phase 3. Contractures with trophic changes of fingers; similar changes in the shoulder not common. Nine years after onset shown in figure 6*d*.

Clinical Forms of Reflex Dystrophy of the Upper Extremity

It has been mentioned that in some cases reflex neurovascular dystrophy of the upper extremity, whether idiopathic or associated with any of the known provocative factors, is evidenced by isolated signs which usually enter into the complete clinical picture of the shoulder-hand syndrome. For example, some patients present only swelling, and finally atrophy, of the hand without shoulder disability; others exhibit painful disability of the shoulder as the sole manifestation; and still others may show contractures of the palmar fascia and/or flexor tendons without additional shoulder or hand

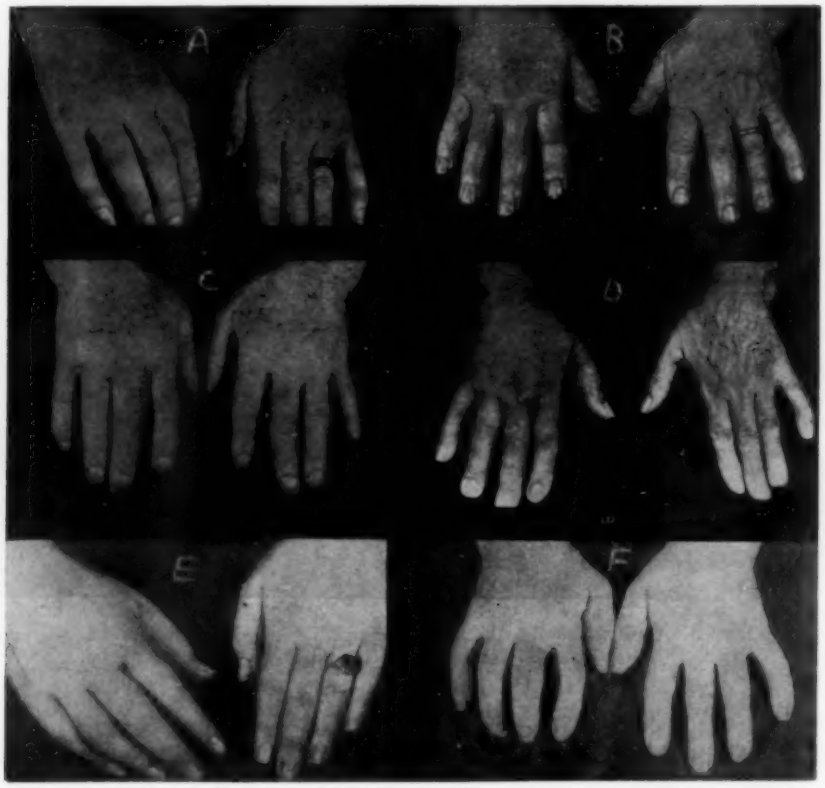

Fig. 6. Clinical similarity of early hand signs with varied causes: (*a*) Weber-Christian disease; (*b*) after herpes zoster of right arm; (*c*) after infectious arthritis of right middle finger; (*d*) idiopathic; (*e*) idiopathic; (*f*) probably post-traumatic.

symptoms. We have seen patients complaining of pain in the upper extremity whose only objective signs were tenderness with vasospasm or vasodilatation of the hand. It has been postulated [38] that some myalgias or fibrositis may represent a circumscribed neurovascular manifestation in the soft tissues. The clinical signs in many cases of rheumatoid arthritis suggest the influence of reflex neurovascular factors.

In many subjects some of these limited features of reflex dystrophy occur as musculoskeletal symptoms without any visceral disease, and cannot be shown to arise as a reflex neurovascular disturbance. Without other characteristic signs or some acceptable precipitating factor, it obviously would be difficult and probably incorrect to classify such instances as reflex dystrophic disorders in the present state of our knowledge. Painful shoulder disability is the most common example.

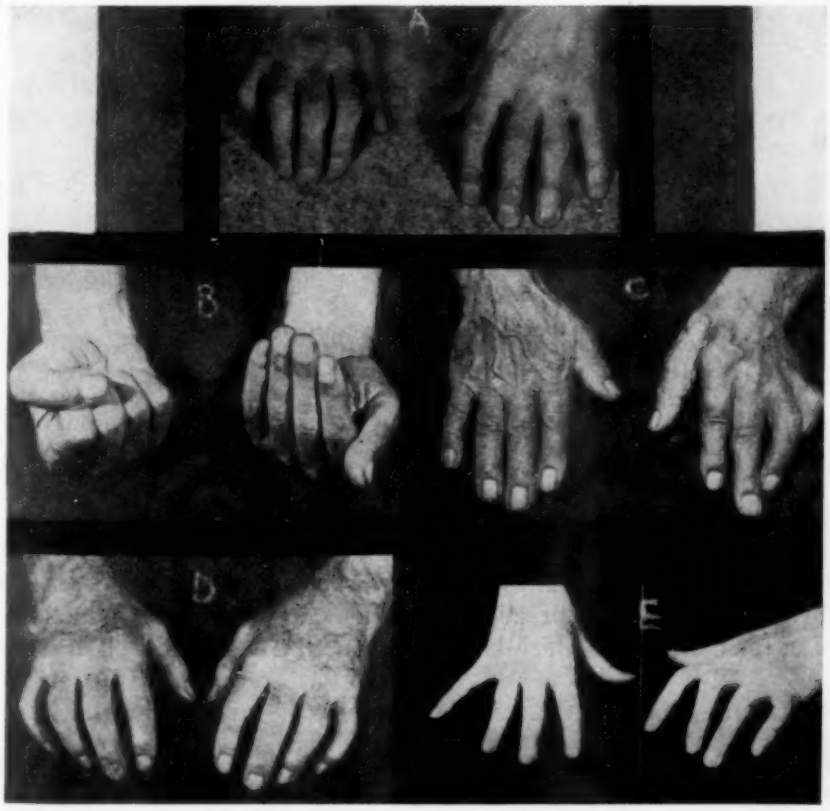

FIG. 7. Clinical similarity of terminal (permanent?) disabling hand signs in (*a*) post-hemiplegic (2 yrs.), (*b*) post-infarctional (9 yrs.), (*c*) idiopathic (3 yrs.), (*d*) post-infarctional, bilateral (1½ yrs.), (*e*) idiopathic (5 yrs.)

Ordinarily, however, the limited manifestations of reflex dystrophy can be distinguished and should be regarded then as incomplete forms of the condition. The partial as well as the more complete symptom-pictures may be due to various causes (table 2). de Takats has described a classification based on the neurone level involved.[8] The etiologic varieties of reflex dystrophy found in our cases are listed in table 3. A number of other underlying diseases not tabulated have been mentioned in the literature—poliomyelitis, syringomyelia, pulmonary infarction and tumors of the cord and

brain. Undoubtedly many additional primary disorders ultimately will be recognized as the source, when a search is made regularly for dystrophic complications.

In two patients observed, but not included in this series, neoplasms in the supraclavicular area produced the shoulder-hand syndrome either as a reflex

TABLE III

Reflex Dystrophy of the Upper Extremity
Etiology in 42 Cases

Idiopathic	11
After myocardial infarction	9
Post-traumatic	5
Post-hemiplegic	5
Post-herpetic	2
Diffuse vasculitis	2
Cervical osteoarthritis	2
Panniculitis	1
Gonococcal arthritis	1
Multiple or inconclusive	4

N.B. 36 cases presented the shoulder-hand syndrome; 6 cases showed only painful swelling and atrophy of hand.

(Some of these cases studied by courtesy of Drs. Russell Cecil, Richard Freyberg, Stewart Gillmor, John Gray, Herman Tillis and C. H. Traeger.)

reaction to infiltration of nerves or ganglia or from compression of sympathetic neural elements. Occlusion of large blood vessels by the enlarging new growth soon adds to the complex clinical picture in such cases. In the early stages of symptoms in these patients, compression of fibers entering or leaving the ganglia, or of ganglionic tissue, produced the picture of sympathetic stimulation, as well as shoulder disability, postulated in reflex dystrophy. These patients practically provide an in vivo reproduction and proof of the mechanism which has been deduced from clinical observation.

INCOMPLETE FORMS OF REFLEX DYSTROPHY OF THE UPPER EXTREMITY

Painful Vasodilatation and Vasoconstriction. Disturbances of the upper extremity characterized by localized painful vasodilatation or vasoconstriction sometimes may constitute incomplete or abortive forms of reflex dystrophy, or they may be the forerunners of more extensive reflex disorders gradually developing. We have observed these symptoms shortly after traumatic lesions and cerebrovascular accidents. A fairly high incidence has been noted recently in poliomyelitis.[39] It is possible that in some disorders of the upper extremity, particularly certain cases designated as scalenus anticus syndrome or as the costoclavicular syndrome, in which pain and vasomotor changes are the outstanding features, a form of reflex dystrophy actually is present. Hyperhidrosis has been an infrequent and minor symptom in our patients.

Contractures of the Palmar Fascia and Dupuytren's Contracture. Dupuytren's contracture [21-26] usually behaves like a benign fibroplasia of the

palmar connective tissue. It may occur in primary form or in association with various diseases. It has been reported as a common sequel to myocardial infarction with or without associated shoulder and hand symptoms.[18-20] For example, contractures of the palmar fascia, in many ways like Dupuytren's, have been found by Askey [19] in seven of 10 cases of post-infarctional shoulder and hand disabilities. Kehl [40] in 1943 reported six cases following coronary occlusion, five of which were associated with shoulder and/or hand symptoms. In the same year Alf Johnson [20] described palmar contractures in 23 of 39 cases of what he termed "post-infarctional sclerodactylia."

Contractures of the palmar fascia and of the flexor tendons in many respects similar to Dupuytren's are common findings in the shoulder-hand syndrome. They also occur in our experience as simple, isolated, uncomplicated features in some cases, as well as in patients with cardiac or pulmonary disease. These palmar changes have been noted by us much more frequently since we have begun to look for them.

The origin of the fascial contractures in the palm is unknown, but they have been considered by some observers, notably Nippert [25] and Powers,[26] to be the result of a disturbance of the sympathetic innervation. Powers [26] states that Dupuytren's contracture is "not an isolated condition nor a clinical entity, but usually an effect of past or present visceral disease." It is related, in his opinion, to scleroderma, hypertrophic pulmonary osteoarthropathy, Raynaud's disease, and other trophic disorders often occurring together. The palmar changes are attributed by him to the irritation and hyperexcitability of the sympathetic nervous system aroused by the underlying visceral disease.

Swelling and Atrophy of the Hand. Swelling and atrophy of the hand unassociated with shoulder disability, with or without palmar contracture, has been observed by us as a sequel to hemiplegia, herpes zoster and trauma to the upper extremity. We have seen this disorder in two patients whose only associated abnormality was cervical osteoarthritis with narrowing of the vertebral foramina by hypertrophic changes. In all of these patients, the temperature changes, pain and trophic features at the hand were consistent with a limited form of reflex neurovascular dystrophy. In our series of 42 cases of reflex dystrophy in the upper extremity, six presented only swelling and/or atrophy of the hand without shoulder involvement.

Painful Disability of the Shoulder. Painful disability of the shoulder as the sole manifestation of reflex dystrophy appears to be a not uncommon aftermath of coronary artery occlusion and hemiplegia. It has also been seen by us in patients with Parkinsonism and after a variety of disabling intrathoracic diseases in elderly people.

The Complete Form of Reflex Dystrophy of the Upper Extremity

The Shoulder-Hand Syndrome. The usual characteristics of the clinically complete form of reflex dystrophy of the upper extremity, the shoulder-

hand syndrome, have already been described. Like the incomplete forms, it may be due to a number of causes enumerated in table 3. Although the signs are comparatively similar in the shoulder-hand syndrome regardless of the basis, some aspects of the clinical picture in each etiologic variety are worthy of comment. Because some of these entities have received little or no attention in the literature, at least recently, a more detailed discussion of their background and distinctive features will be presented.

We refer to the "clinically complete" form of reflex dystrophy when the shoulder and hand are affected, because it represents the most extensive reflex symptom-complex ordinarily seen. We have encountered only two patients with the shoulder-hand syndrome presenting symptoms at the elbow joint. For some reason, not clear at present, this articulation and its connected structures usually escape involvement. The use of the term "shoulder-hand syndrome," then, is intended to imply a reflex neurovascular disturbance of which shoulder involvement is an important sign. Somehow this feature seems to have gone unrecognized as a further manifestation of the reflex mechanism even in the latest publications.

In several of our patients the shoulder symptoms had resolved when they finally sought relief of the hand complaints. The complete evolution of the clinical picture then would have been missed without a thorough history.

The classic concept of reflex neurovascular dystrophy following some form of external violence has been established so firmly by Sudeck's description of post-traumatic osteoporosis that a history of trauma has come to be expected or assumed when trophic symptoms are encountered in an extremity. In medical conditions complicated by reflex dystrophy we are actually confronted with internal irritation or injury as the precipitating factor. It must be concluded, therefore, that the similar clinical pictures seen with the varied etiology considered here may be produced by either internal or external tissue trauma acting through an identical neurophysiologic mechanism to be discussed later.

Etiologic Varieties of Complete Reflex Dystrophy of the Upper Extremity

The Idiopathic Shoulder-Hand Syndrome. The idiopathic variety, which we wish to emphasize especially, has exhibited the shoulder-hand syndrome in its complete form in all of our cases so far. No etiologic factor has been found in any of the 11 patients who comprise this group, nor has there been any history of injury. Undoubtedly in many such instances the signs have gone unrecognized in the past or have been assumed to follow some minor trauma to the extremity even when the patient could not recall any. In other cases the most striking symptoms were attributed to acute bursitis, periarthritis, scalenus anticus syndrome, atypical rheumatoid arthritis, non-specific infectious arthritis, gout or scleroderma, according to the stage of the disorder.

As a result of Sudeck's original description of the neurovascular syndrome due to suppuration or external trauma, even in the definite absence of a history of injury, an unnoticed or forgotten sprain or torsion is more apt to be taken for granted as the etiologic factor in many patients with merely "spontaneous" complaints. For example, "spontaneous" symptoms of unknown etiology have been mentioned by Noble and Hauser [4] as occurring in 12 of the 48 cases of acute bone atrophy reported by them. Undoubtedly these would fall into our idiopathic group. So long as a definite, provocative factor is not demonstrable, it is probably desirable to keep these patients segregated as presenting a distinct "idiopathic" entity.[33a] Some definite physiologic abnormality or incipient pathology underlying this clinical picture, so far unrecognized, may be established in future. Studies on costoclavicular and neurovascular disorders of the shoulder arising from mechanical, vascular and developmental defects at the thoracic inlet in time may explain some of these idiopathic cases.[42-44] Until a fund of information acquired by postmortem and surgical exploration of more of these subjects with "spontaneous" symptoms accumulates, as in the recent study of Telford, our information must remain inadequate to explain the cause of the idiopathic disorder and its basis must be considered unsettled.

The Shoulder-Hand Syndrome, Post-Traumatic

Causalgia. This condition and its relation to Sudeck's atrophy and other forms of reflex dystrophy have been discussed extensively by de Takats,[5-8] Livingston,[2] and others.[34, 35] It was first described by Weir Mitchell,[1] occurring as an occasional sequel to injury of a peripheral nerve (most commonly the median nerve), characterized by the following symptoms: (1) the presence of severe, constant, throbbing or burning pain in the affected limb; (2) exquisite cutaneous hyperesthesia with extreme hypersensitivity to the environment, so severe that the lightest stimulus or emotion will induce agonizing paroxysms of pain; (3) extensive trophic changes, especially glossy skin; and (4) variable cutaneous temperature and other vasomotor disturbances. The impression is inescapable in these cases that there often exists a superimposed psychogenic factor as well. Causalgia, therefore, is a form of reflex dystrophy occurring in association with injury to a peripheral nerve, in which burning pain and hypersensitivity to stimuli are the outstanding features. One patient in our series could be classified in this category.

Minor causalgia is a term coined by Homans [3] to describe a form of reflex dystrophy in which pain is a less conspicuous feature than in true causalgia, but in which the symptomatology is otherwise similar.

Post-Traumatic Osteoporosis (Sudeck's Atrophy)

The bone atrophy which bears his name was first established as a definite clinical entity by Sudeck [9] in 1900. In 1877 and in 1883, Wolff [45, 46] had

described the occurrence of trophic changes in the limbs of patients following infection or resection of a joint. He then originated the theory of an underlying trophoneurosis. In 1895 Kümmell [47] reported six cases of bone atrophy following slight trauma. Additional papers by Sudeck [10, 11] and Kienböck [48] appeared in 1902. They further clarified the clinical picture and gave accurate roentgenologic descriptions of the bony changes. They showed clearly that inactivity alone could not account for the degree of bone atrophy observed, that it appeared long before the atrophy of disuse, and even occurred in certain cases while the limb was in use. Originally Sudeck felt that the condition was inflammatory in origin but later subscribed to Kienböck's view that it was a trophoneurosis. Sudeck's atrophy subsequently received considerable attention from German authors, and to a lesser extent from the French, especially Leriche [49] and his co-workers. Noble and Hauser's paper [4] in 1926 was the first reference to this subject in the English and American literature. Since then many reports have appeared, notably those of Fontaine and Hermann,[50] Gurd,[51] Hermann and Caldwell,[52, 53] de Takats and Miller,[5-8] and Sweetapple.[41]

Sudeck's atrophy, otherwise known as post-traumatic osteoporosis, acute bone atrophy, peripheral trophoneurosis, etc., when it involves the upper extremity, is undoubtedly a form of reflex dystrophy. It may affect the upper or lower extremity. It occurs also in the spine.[4] The condition has been reported after minor fracture, injury or sprain, often about the wrist or ankle joint. Generally, the first clue to its recognition is the appearance of severe, constant throbbing or burning pain with paroxysmal exacerbations, in a patient whose injured limb, to all appearances, is properly immobilized, uninfected and healing satisfactorily. Placing the part in a cast or support aggravates the pain. The onset usually occurs within two weeks of the time of injury. More rarely it follows a suppurative lesion of the limb. The pain then ushers in the train of symptoms and signs already described as characteristic of reflex dystrophy. Sudeck's atrophy of the upper extremity represents a variety of the shoulder-hand syndrome, due to trauma or suppuration, when clinically complete signs arise. Incomplete reflex symptoms are common here.

The Shoulder-Hand Syndrome, Post-(Myocardial) Infarction

For some years clinicians have been aware of the occurrence of persistent painful shoulder disability following coronary occlusion.[1] Almost 50 years ago Osler mentioned the "motor disability" at the shoulder observed by him in some patients after "anginal attacks." [13a] In 1930 Howard reported five cases illustrating the presence of a stiff, painful shoulder simultaneously with, or following, severe myocardial disease. He emphasized the importance of recognizing this association for two reasons: (1) the pain of "periarthritis" of the shoulder might be mistaken for severe cardiac pain, or (2) the shoulder lesion might receive attention while the changes in the heart are overlooked. The shoulder disability was regarded by him as

basically a "periarthritis" resulting from referred pain with attendant partial immobilization, loss of tone, mechanical maladjustments, and secondary inflammatory changes. He thought that this combination of shoulder dysfunction and cardiac disorder was so frequently encountered that a causal relationship was suggested.

Libman [14] likewise noted the frequent co-existence of shoulder pain and angina pectoris. It was his opinion that they were both caused by the same metabolic disorder. He pointed out that a "subacromial bursitis" will not infrequently begin shortly after a coronary thrombosis has occurred.

In 1936 Edeiken and Wolferth [15] reported 14 cases with persistent shoulder pain following myocardial infarction, appearing coincidentally up to 16 weeks following the heart attack, and lasting weeks to years. They found the condition unilateral or bilateral, most frequently the former. The cardiac lesion was considered by them to be an important etiologic factor. It was their impression that the incidence of this symptom among survivors from infarction might exceed 10 per cent. To them the symptomatology suggested "an analogy to causalgia." They found neither local nor roentgen-ray therapy of any value in treatment.

Boas and Levy [16] in 1937, and Leech [17] in 1938, also reported observing a painful stiff shoulder in patients with coronary artery disease. Boas and Levy postulated two possible mechanisms for the shoulder disorder: first that radiation of the anginal pain to a shoulder already the site of slight pain might, by summation, produce the painful disability: and second, that the afferent pain impulses from the heart might sensitize neurons whose fibers enter into the brachial plexus.

Ernstene and Kinell noted the occurrence of persistent pain in one or both shoulders as a relatively common sequel to myocardial infarction.[18] They found 17 cases of persistent pain in the shoulder region in a series of 133 consecutive cases of myocardial infarction. In six of their 17 cases symptoms of "rheumatoid arthritis" involving the hand joints developed simultaneously with, or subsequent to, the shoulder symptoms. The "remarks" for two of their cases indicate that the authors had observed changes in the hand and fingers not unlike those described for reflex dystrophy. They did not, however, relate the hand changes to the shoulder disability. It is interesting to note here Osler's reference in 1897 to Eichhorst's observation that some of his patients had presented "atrophy of the muscles of the hand" after anginal attacks.[13a] Recently ulcerative lesions of the digits after myocardial infarction have been reported.[13c]

Askey regarded the combination of hand and shoulder symptoms following infarction as a definite syndrome.[19] He reported 22 cases illustrating the combined symptoms and clearly described the shoulder disability and hand changes that are the subject of this paper. He found Dupuytren's contracture in seven of 10 cases examined for this particular condition. Askey looked upon the hand involvement as an extension of the shoulder disability previously described by others. He believed that the syndrome is

related to myocardial infarction and is caused by a "combination of sympathetic disturbance and arthritis, with varying degrees of preponderance of one or the other." He was careful to state, however, that "the course of the hand disability was characteristic of neither long-standing rheumatoid arthritis nor osteoarthritis."

In 1943 Johnson reported a series of 39 patients, of 178 consecutive cases of myocardial infarction, who exhibited trophic changes in the hand resembling "sclerodactylia." Thirty-four of these also showed unilateral or bilateral shoulder pain and disability. He accurately described the hand changes which he believed to be analogous to those occurring in Raynaud's disease and scleroderma. Hence he suggested for them the name of "post-infarctional sclerodactylia." He did not consider the shoulder symptoms to be related to the hand changes or to be of the same etiology. They were regarded by him as the result of voluntary or involuntary splinting of the joint. The hand changes, he thought, were due chiefly to ischemia of reflex origin, augmented by local anoxemia due to arteriosclerosis and systemic anoxemia of cardiac origin.

The clinical pattern of the post-infarctional type of shoulder-hand syndrome resembles that due to other causes. Typically, the dystrophic process has its onset three to 16 weeks after acute myocardial infarction or following long-standing angina pectoris. The shoulder disability generally, but not invariably, precedes the changes in the hand by an interval of a few weeks. Usually, the symptoms are bilateral but unilateral localization at either the right or left upper extremity is not uncommon. The question of whether the side of radiation of the cardiac pain predisposes to the subsequent localization of the syndrome is at present unsettled by the conflicting reports in the literature on this point. The occurrence or localization of the symptoms bears no relationship to the site of myocardial infarction. They appear following both anterior and posterior wall involvement. The additional development in some of these cases of contractures of the palmar fascia and of typical Dupuytren's contracture has already been discussed.

This etiologic variety of the shoulder-hand syndrome has been found by us most frequently to run a stubborn course. Most of our cases were seen, however, in the later stages.

The Shoulder-Hand Syndrome, Post-Hemiplegic

Ever since Chevallier's report in 1867, it has been recognized that vasomotor changes are often present in extremities paralyzed by cerebral lesions. From a brief survey of the literature on hemiplegia for symptoms characterizing reflex dystrophy it is apparent that many of the features which are typical of this complication have been observed in the paretic limbs of some hemiplegics.[28-32] The changes recorded include particularly swelling, changes in skin temperature, vasomotor disturbances, and, in rare instances, trophic changes. "Arthritic changes, especially in the shoulder" [54] have

also been noted as an interpretation of the unusual stiffness and limited mobility which may develop. Yet in none of the reports of these observations have they been recognized as a form of reflex dystrophy. The only references to this point in the literature to our knowledge, are statements by de Takats [8] and Evans [34, 35] that causalgic states may follow cerebral lesions. de Takats [8] mentions one case of cerebral thrombosis and Evans [34, 35] lists one of a thalamic syndrome, each of which was followed by reflex dystrophy.

In hemiplegia the vascular lesion which destroys the motor functions, undoubtedly, likewise interferes with the control of the autonomic nervous system normally exerted by the higher centers. In that way it may predispose to the subsequent development of the shoulder-hand syndrome. Indeed, the paretic limb frequently presents the symptoms of a mild form of reflex dystrophy which in most cases undergoes spontaneous resolution. In some instances, however, far more often than has been recognized, the changes are progressive and the florid picture of reflex dystrophy of the upper extremity develops. We have observed four individuals with the post-hemiplegic shoulder-hand syndrome within a short period. Reflex changes may occur in the lower extremity. Oddly enough, shoulder disability is a less prominent characteristic of this variety of reflex dystrophy, probably due to masking by the paralysis. Furthermore, in two of these patients we have found pain, tenderness and limitation of motion at the elbow. Symptoms at this joint have not been observed by us so far in any of the other etiologic varieties of reflex dystrophy. The remaining features presented by these subjects follow the pattern already described.

The Shoulder-Hand Syndrome, Post-Herpetic

In 1938, Marques reported a case of osteoporosis following an attack of herpes zoster brachialis. He pointed out the rarity of the observation. His patient presented the usual symptoms of the dystrophic process with roentgenologic changes in the hand "characteristic of Sudeck's atrophy." He noted the similarity to post-traumatic osteoporosis as described by Leriche, Fontaine and their co-workers. The only other reference to this condition in the literature that we have been able to find is a statement by de Takats [8] that herpes zoster may be complicated by reflex dystrophy. We have observed two patients in whom neurovascular dystrophy has followed, by three and six weeks respectively, an attack of herpes zoster of the now affected upper extremity. Their symptoms were typical for the hand involvement, although they recall no shoulder disability.

The Shoulder-Hand Syndrome, Secondary to Cervical Osteoarthritis

In 1938 Oppenheimer [37] reported a series of 14 patients with swelling and atrophy of the hand associated with radiologic evidence of intraforaminal

constriction at one or more of the upper four cervical vertebrae. The encroachment on the interspaces he found to be secondary to one of the following: degenerative disc disease with, or without, intraforaminal exostoses; previous compression fractures or subluxations of the vertebrae; or simple reduction of the intervertebral lumen by osteoarthritic spurs.

All of the patients had been troubled with recurrent "rheumatic pains" in the shoulder region of the affected side, and by paresthesias in the fingers for periods of several weeks to 20 years. Oppenheimer apparently did not relate this shoulder pain to the condition of the hand, nor did he mention tenderness or any limitation of function at the shoulder. Six of the cases showed osteoporosis of the hand. He concluded that of seven patients treated with ultra-short wave diathermy to the cervical spine, he effected a remission of symptoms in six. He did not correlate the condition described by him with any other disorder, nor did he elucidate the basis for the development of atrophic swelling of the hand from the cervical osteoarthritis seen in his roentgen-ray films.

It is clear from the foregoing discussion that the disorder described by Oppenheimer represents a limited form of reflex dystrophy attributed by him to intraforaminal constriction in the cervical spine of osteoarthritic, discogenetic or traumatic origin. Although our patients, so far, have represented largely the older age groups, the absence of any demonstrable abnormality in the cervical spines of many of these cases reasonably excludes osteoarthritic pathology as a uniform predisposing factor in the shoulder-hand syndrome, if at all. One of our patients, a 15 year old female, showed the normal cervical spine to be expected at that age.

The Shoulder-Hand Syndrome, Secondary to Vasculitis

The systemic angiopathies such as periarteritis nodosa and diffuse arteritis, as a result of lesions in the periphery or possibly in the spinal cord and ganglia, or even localized thrombophlebitis, may provoke classic reflex dystrophy as a complication. We have studied two such cases with diffuse arteritis and Evans has reported one.

The Shoulder-Hand Syndrome, Secondary to Nodular Panniculitis

We have observed one patient with febrile, relapsing, non-suppurative, nodular panniculitis (Weber-Christian) complicated by neurovascular dystrophy. The only pannicular invasion of the upper extremities had consisted of a solitary nodule in the deltoid area on the dystrophic side. This lesion was followed in a few weeks by insidious development of the shoulder-hand syndrome which had persisted about five months after the bout of nodular panniculitis had resolved. To our knowledge this is the only instance of reflex dystrophy as a complication of Weber-Christian disease.

Mechanism of the Shoulder-Hand Syndrome

Studies on the dynamics of this disorder have concerned largely the traumatic cases. These have consisted of attempts to explain the obvious vasomotor changes and the distinctive types of pain seen in the post-traumatic syndrome. The peripheral, injured area has been accepted as the site of origin of afferent stimuli with the sympathetic system as the efferent branch of the reflex.[2, 5, 34, 35, 49, 50]

According to the rapidly growing impression, external trauma constitutes only one source of reflex dystrophy. As we have stated, the syndrome arises from many different causes. A more inclusive physiologic clarification, therefore, is in order. It must take into account these pertinent clinical facts: (1) conditions of widely separated location, such as myocardial infarction, herpes zoster, peripheral injuries, etc., can cause practically the same clinical picture; (2) this disorder seems to involve not only the autonomic system, parasympathetic as well as sympathetic, but also the motor pathways to muscles; (3) the disturbance does not show a definitely segmental distribution; and (4) it is often improved or abolished by interruption of the sympathetic nerve supply to the upper extremity.

Any working explanation of the reflex mechanism must remain hypothetical to a great extent, since it must depend on some of the current concepts in neurophysiology which cannot be verified by clinical methods to the exclusion of all the others. An abundant literature supports the idea of an axone reflex and/or of antidromal stimulation from a focus of irritation or injury. However, the probable rôle in this syndrome of the internuncial pool, as developed by Lorente de Nó [55] and elaborated by Livingston,[2] appears to offer the clearest understanding of its dynamics. The clinical picture seen in the shoulder-hand syndrome embraces a medley of signs and symptoms which must be effected through the autonomic, more noticeably the sympathetic, and cerebrospinal outflows of several cervical and thoracic spinal segments. The afferent stimuli may be assumed to arise in a general way from a focus of physiologic irritation or from a local, injured area in the extremity, the heart, the cortex, etc.—any site of external or internal disturbance or violence to tissue (figure 8).

In many cases, as for example in cerebral lesions, the afferent stimuli must enter cord segments far removed from those supplying the upper extremity. Owing to this fact and to the rather diffuse nature of the signs in the shoulder-hand syndrome, the segments involved usually defy accurate neurologic localization. The mechanism can be readily conceived, however, as a widespread disturbance of the internuncial pool. Recent neurophysiologic investigation [55] shows this pool to be an extensive network of interconnecting neurones in the central gray matter, extending over many segments. At these levels potential connecting pathways are formed between incoming impulses and motor neurones of either the sympathetic (posterolateral) or anterior horn cells.

The internuncial disturbance may be visualized as arising in this manner: Following a myocardial infarction, for example, afferent stimuli traverse the cardiac nerves to enter the cord at levels T_1–T_4. These new and profound stimuli strongly activate the internuncial pool in that area of the cord. The

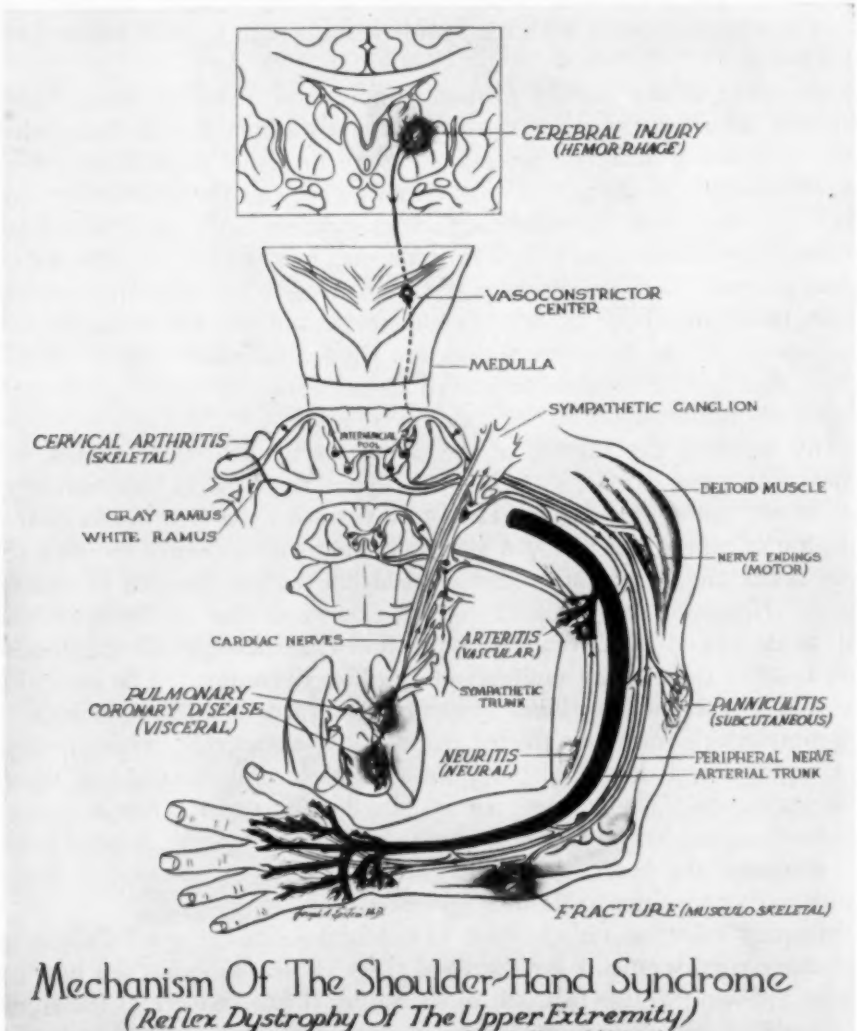

FIG. 8. A diagrammatic representation of current neurophysiologic concepts applied to the shoulder-hand syndrome and some of its causes.

disturbance spreads upward with effects on the anterior horn cells, causing disability of the shoulder muscles. It travels downward to involve the sympathetic neurones of the lateral horn cells innervating the upper extremity. The continuous activity of the internuncial pool and the chronicity

of the shoulder-hand condition may be due to self-exciting, and self-perpetuating, closed chains established at various points in irregular fashion, as described by Lorente de Nó. The severity of the symptoms would depend on the intensity of the stimuli and rate of discharge of the chains of irritation. This diffuse involvement upward and downward of spinal cord segments would account for the fact that specific myotomes and dermatomes do not seem to be selectively affected in this syndrome rather than a good part of the upper extremity as we find.

The next consideration in discussing the mechanism of reflex dystrophy must be the beneficial results obtained from local interruption of the sympathetic system. Many of the clinical features clearly point to a neurovascular imbalance, predominantly of the vasomotor system. In the first stage of the disturbance, as already described, the hands are apt to be warm and swollen. This elevated surface temperature ordinarily is acknowledged to indicate an increased blood flow. Confirmatory evidence of this principle has been advanced by de Takats [5, 7] in his observations on post-traumatic dystrophy. He reported that oscillographic pulsations are augmented. At the same time plethysmographic records show an increased blood flow in the affected extremity. Ellis and Weiss [32] studied hemiplegias complicated by the features regarded by us as the shoulder-hand syndrome. They found in most of them, by measurement of arterio-venous differences, that the blood flow was increased on the dystrophic side.

In the later stages of the syndrome a different type of vasomotor disturbance is present. The hand is generally cold. The skin appears thin and atrophic. Ischemia completes the evidence of vasoconstriction. Leriche,[49] who has written extensively on the subject, believes that trauma produces an instability of the autonomic nervous system which may lead to alternating and intermittent stages of vasoconstriction and vasodilatation. Either of these vascular phenomena, in his opinion, may persist as a chronic disorder.

In the later stages of the shoulder-hand syndrome, with the onset of trophic changes and diminished temperatures, the reason for the benefit from sympathetic block is fairly obvious. As a matter of fact, however, best results are obtained in the first phase, when the hand is warm and already shows evidence of an increased blood flow. The use of nerve block here seems paradoxical. Miller and de Takats [5] found that after sympathetic block the already augmented blood flow on the dystrophic side was further increased. These aspects of the underlying physiologic mechanism require further clarification.

The osteoporosis, which may develop early, probably represents an initial result of the hyperemia found in the early phase. It has long been known that bone atrophy follows any prolonged, deep hyperemia. It is unlikely that the decalcification found in this condition arises merely as a disuse atrophy. It has been demonstrated that disuse atrophy is a general decal-

cification that takes a much longer time to appear than the short interval peculiar to the disorder under discussion.[10, 11, 48, 56] Moreover, the osteoporosis of reflex dystrophy, as we have stated, is observed to develop in limbs that are functioning.

The pain of the shoulder-hand syndrome, particularly in the post-traumatic varieties, is attributed to stimulation of regular pain afferents in the vicinity of the traumatized or damaged area. It must be recalled, however, that an autonomic disturbance appears to be part of the "vicious circle" which maintains a state of irritability at the termination of the pain receptors, possibly by altering local metabolites, in that way leading to continuous stimulation or "bombardment" of the internuncial pool of the spinal cord.[2, 49, 55] When the efferent elements of this circuit, especially the sympathetic fibers, are interrupted, the "vicious circle" is broken and its attendant pain abolished. The relief of disability and muscle spasm following sympathetic block in these cases may be explained on the same basis. Despite the paradoxical features, difficult to clarify entirely in the present state of our knowledge, the fact remains that, empirically, interruption of the sympathetic nerve supply to the limb relieves pain, resolves the signs and restores function in the majority of cases with impressive rapidity.

The Differential Diagnosis of the Shoulder-Hand Syndrome

It is important for many reasons to distinguish all forms of reflex dystrophy of the upper extremity from the many conditions they may resemble. Because the reflex signs in the limb may happen to be those first noticed, before the confirmatory evidence of disease in the thoracic viscera, brain, cord or regional musculoskeletal structures, their early, correct interpretation assumes great diagnostic importance. From a therapeutic standpoint the effective, early use of proper measures and the avoidance of strenuous treatment, employed in the diseases with which reflex dystrophy may be confused, make differential diagnosis an especially imperative consideration here.

The limitations of space permit us to discuss only the differential diagnosis of the complete form of reflex dystrophy, the shoulder-hand syndrome. The early stages of reflex shoulder involvement, particularly when acute and subacute, resemble bursitis and periarthritis (periarticular fibrositis). The local signs—pain (sudden or insidious), diffuse tenderness and disability in all ranges of motion—are similar to those seen in the uncomplicated peripheral disorders of the shoulder. When a history of visceral disease or evidence of severe cervical intraforaminal constriction is presented, the probability of incipient or incomplete reflex dystrophy must be suspected, appearing in many cases as the fore-runner of the complete clinical picture. The onset of hand signs usually resolves any doubts and completes the evidence of the shoulder-hand syndrome. In some of the patients with prolonged shoulder disability scapulohumeral fixation seems to develop.

The chief resemblance to the scalenus syndrome lies in the tenderness of the scalenus muscles in some of these patients, along with other points of soreness in the neck and shoulder, with weakness of the grip when the hand is swollen. Injection of the scalenus anticus muscle with procaine has proved ineffective. In the rare cases reported of scalenus anticus syndrome associated with hand signs similar to those in reflex dystrophy, it is quite likely that compression of the cords of the brachial plexus or of the subclavian artery has provoked reflex neurovascular symptoms as a complication. The possibility that the swelling of the hand represents partial occlusion of an anomalous subclavian vein running beneath the scalenus anticus muscle, instead of over it, was not confirmed in one patient subjected to exploration.

The appearance of the hand and fingers in the shoulder-hand syndrome is merely suggestive of rheumatoid disease in the early stages, particularly atypical rheumatoid arthritis. The swelling of the hand and digits is uniform, affecting all of them diffusely, rather than being limited to the periarticular tissues of one or merely several metacarpophalangeal or proximal interphalangeal joints. Tenderness to palpation, too, is generalized, and it is elicited anywhere on the hand. The persistent homolateral involvement of the shoulder and hand without symptoms in other joints on the same or on the opposite side of the body is unlike the behavior of rheumatoid arthritis. Only one of our patients seen in early phase I showed an increased sedimentation rate which soon became normal despite the progression of her condition. Even in the early stages of reflex disorders, the patients are afebrile and we have not found a leukocytosis.

Gout is simulated in very early hand involvement, by severe, painful, pinkish or pale swelling of the whole hand. The repeatedly normal blood uric acid, the unresponsiveness to therapy for gout, and surely a history of trauma or evidence of high visceral disease or other etiologic factors already stated, should suggest the probability of reflex dystrophy.

The appearance of the hand in the late stages has been regarded by some as the equivalent of scleroderma. This is not the place to consider the argument as to whether the latter condition may be due to reflex sympathetic changes. Our early cases have been characterized by a generalized swelling of the peripheral tissues, including the skin. Later, atrophy of all the structures of the fingers and hand develops gradually with, finally, striking trophic changes in the skin and underlying subcutaneous tissues. The skin becomes thin, smooth, glossy and in some patients presents remarkable hypertrichosis over the dorsal surface of the proximal phalanges. We have not observed the rigid, thickened cutis with pigmentation so characteristic of long-standing scleroderma. The frequent contractures of the palmar fascia and tendons is a typical concomitant in the late trophic stages of the shoulder-hand syndrome.

Treatment of the Shoulder-Hand Syndrome

The management of these disorders until recently has proved largely unsatisfactory. Numerous forms of therapy, therefore, have been recommended for reflex dystrophy. The latest developments in sympathetic nerve block and in sympathetic surgery represent a great and highly effective advance in the treatment of these conditions.

Orthopedic and Physio-Therapeutic Measures

Immobilization of the affected parts in conjunction with the various modalities of physiotherapy—heat in all forms, heliotherapy and massage, have been utilized extensively. These measures, however, apart from giving temporary palliation, seem to exert little influence on the course of the disease. Oppenheimer,[37] on the other hand, employed short-wave diathermy to the cervical spine and in six of seven cases with swelling and atrophy of the hand secondary to cervical osteoarthritis he reported recovery. Our results with this form of treatment have not been impressive.

Manipulative procedures have been widely condemned. Manipulation of the shoulder, especially, in these cases is apt to be based on a misdiagnosis of bursitis, fibrositis and, possibly, scalenus anticus syndrome. The shoulder discomfort and disability frequently are regarded as symptoms complicating, or unrelated to, the hand signs. According to our experience such deductions usually represent a failure to correlate the salient features of the shoulder-hand syndrome.

Radiation Therapy

Mumford[57] treated six cases of Sudeck's atrophy with high-voltage roentgen therapy to the affected extremity and reported good results in five. Hermann et al.,[53] however, subjected 18 patients with acute osteoporosis to radiation therapy, as outlined by Mumford and found that, while the pain was greatly lessened or relieved, the osseous changes, the disturbed function and the period of disability, were not materially influenced. We have had no experience with this type of treatment, although we have used radiation therapy directed to the cervico-dorsal region of the spine and to the sympathetic ganglia without benefit in three patients.

Block Therapy

Block therapy with procaine or related anesthetic drugs has been recommended in the form of: (1) local injections at the "trigger points" and (2) infiltration of the appropriate sympathetic ganglia.

It would seem that local injections at the site of injury or irritation in post-traumatic reflex dystrophy should exert a beneficial action by blocking the afferent painful impulses, with consequent breaking of the "vicious circle"

already in action. Repeated local procaine injections of the injured area, however, have proved unsatisfactory in many instances. These unfavorable results arise usually from the difficulty in locating the "trigger points" exactly and from the widespread nature of the dystrophic symptoms and signs.

Excellent results have been reported from paravertebral sympathetic infiltration with procaine or related substances for reflex dystrophy of varied etiology. For example, of eight patients treated only with repeated sympathetic blocks, de Takats [8] observed complete recovery in seven, and partial recovery in one. Evans [35] reported arrest of symptoms or considerable improvement in all of 12 patients treated only with sympathetic blocks.

The newer technics of administering stellate and upper dorsal ganglion blocks by the anterior or anterolateral approaches, without necessitating hospitalization, constitute real progress in these therapeutic procedures.[59] In addition to sympathetic ganglion infiltration, brachial plexus block has been employed by us. Following plexus block shoulder disability improves often, but the hand signs are not influenced by this procedure. Adequate sympathetic response evidently cannot be effected by this approach. Shoulder signs resolve spontaneously much more often than the hand changes, so that treatment must be based on the responsiveness of these most serious features lest trophic alterations develop, after which repeated sympathetic block is not as apt to be successful as in the early phase.

Surgery

Sympathetic surgery is employed in reflex dystrophy, when repeated sympathetic blocks give only partial relief of symptoms, or when the response is effective but not lasting. The patient's general condition must be suitable. Several procedures are available: periarterial sympathectomy, sympathetic ramisection and ganglionectomy. Leriche,[49] Fontaine and Hermann [50] recommended the first operation when the disease is localized, and ganglionectomy when the process is more widespread. They reported good results with these operations. The success of periarterial sympathectomy and sympathetic ganglionectomy in these conditions has been confirmed in the exhaustive studies of de Takats.[5-8] He obtained complete recovery in eight of 12 patients so treated, and improvement in four. Evans [35] reported a satisfactory outcome in 22 of 29 patients who underwent sympathectomy. If sympathectomy fails, and pain continues unrelieved, anterolateral cordotomy and possibly sensory denervation of the cortex merit consideration, usually for intractable causalgia.[44]

Recently tetraethyl ammonium salts which cause blockade of the autonomic ganglia, have been suggested for pre-surgical therapeutic tests and for treatment of the causalgic states.[60] It is as yet too early to evaluate this mode of therapy.

Therapeutic Recommendations

Precise conclusions from our own experience with therapy will be published in detail elsewhere.[58] From the data on hand, however, it would appear that the treatment of choice for *Phase I* is stellate, and possibly also upper dorsal, sympathetic ganglion block. For *Phase II* this treatment is worth a trial. Even in *Phase III* it may at least provide relief of pain, especially when surgery is contraindicated by the general condition of cardiacs and hemiplegics. The desirable time for sympathectomy is during *Phase II* or earlier.

Spontaneous recovery from shoulder disability and pain especially, and in some cases also from the trophic changes, may occur before, or during, this stage. The ultimate course of any individual, however, is unpredictable. Failure to initiate proper treatment as early as possible frequently subjects the patient to the eventual hazard of more drastic measures or to irreversible, disabling alterations in the extremity.

From the onset through *Phase II*, therefore, we employ repeated sympathetic blocks with procaine or similar substances. When these give only partial relief of symptoms, or if the benefits prove only temporary, sympathetic surgery is indicated, provided the patient's general condition permits. Sympathetic blocks serve in that way not only as a method of treatment, but also as a therapeutic test for the proper selection of cases likely to respond to sympathectomy. When repeated sympathetic blocks, properly performed, are completely unsuccessful, it is uncertain whether sympathectomy will prove any more effective in relieving the symptoms. In *Phase III* sympathetic block for pain supplemented by intensive physical rehabilitation measures within the limits of the patient's reserve are warranted to retain, possibly to increase, the degree of function of the dystrophic extremity. Following relaxation by heat, special exercises to maintain mobility of the joints are employed by us at all stages when they do not provoke additional discomfort. In the late cases rehabilitation by retraining of muscular and digital function may reduce the disability.

Relapses

Only one of the patients in our series gave a history of a previous attack of idiopathic painful swelling of the hand. It cleared up spontaneously over several months without any residual changes. About five months later she developed the shoulder-hand syndrome which resolved following three stellate blocks in the course of two weeks. This patient recently again presented a spontaneous, acute swelling of the hand alone, about seven months after treatment, which cleared up after one block. Obviously the incidence of relapses may prove greater than the present limited follow-up period reveals.

Summary

1. A number of seemingly different disorders, frequently involving the upper extremity, including the idiopathic shoulder-hand syndrome, described in the surgical and medical literature as separate entities appear to be closely related.

2. Although their etiology or precipitating factor varies, these conditions exhibit clinical features which are quite similar and the underlying mechanism seems to be identical, a reflex neurovascular dystrophy.

3. The different disorders embraced in reflex dystrophy of the upper extremity present either incomplete or complete signs of the neurovascular reaction of which the shoulder-hand syndrome constitutes the most complete picture.

4. The variable clinical features and the differences in the severity of symptoms probably are due to different degrees of reflex neurovascular and motor reaction.

5. Among these clinical pictures of reflex dystrophy, especially the idiopathic shoulder-hand syndrome, the shoulder disability and hand signs are often not correlated in the diagnosis, and are apt to be given separate diagnoses for the shoulder disability and for the hand signs.

6. The current neurophysiologic concept of "a vicious circle" mediated through an internuncial pool of active stimuli in the cord, provoked and maintained by the primary precipitating condition, explains the mechanism common to all forms of reflex (neurovascular) dystrophy, regardless of etiology. It serves as a useful working basis for the present therapeutic approach.

7. Treatment by sympathetic interruption (with stellate and upper dorsal ganglion block or surgery) is effective in a great number of all etiologic varieties, in that way confirming the common identity of the underlying mechanism.

8. Therapeutic results depend on the phase or stage of the disorder and the selection of the proper procedures.

BIBLIOGRAPHY

1. Mitchell, S. W., Morehouse, G. R., and Keen, W. W.: Gunshot wounds and other injuries of nerves, 1864, J. B. Lippincott, Philadelphia, 164 pages.
2. Livingston, W. K.: Pain mechanisms: a physiologic interpretation of causalgia and its related states, 1943, The Macmillan Company, New York.
3. Homans, J.: Minor causalgia: a hyperesthetic neurovascular syndrome, New Eng. Jr. Med., 1940, ccxxii, 870–874.
4. Noble, T. P., and Hauser, E.: Acute bone atrophy, Arch. Surg., 1926, xii, 75–94.
5. Miller, D. S., and de Takats, G.: Post-traumatic dystrophy of the extremities—Sudeck's atrophy, Surg., Gynec. and Obst., 1941, lxxv, 558–581.
6. de Takats, G., and Miller, D. S.: Post-traumatic dystrophy of the extremities—a chronic vasodilator mechanism, Arch. Surg., 1943, xlvi, 469–479.

7. DE TAKATS, G.: Nature of painful vasodilatation in causalgic states, Arch. Neurol. and Psych., 1943, l, 318–326.
8. DE TAKATS, G.: Causalgic states in peace and war, Jr. Am. Med. Assoc., 1945, cxxviii, 699–704.
9. SUDECK, P.: Ueber die akute enzündliche Knochenatrophie, Arch. f. klin. Chir., 1900, lxii, 147–156.
10. SUDECK, P.: Ueber die akute reflektoris Knochenatrophie nach Entzünden und Verletzungen an den Extremitäten und ihre klinische Erscheinungen, Fortschr. a. d. Geb. Röntgenstr., 1901–1902, v, 277–293.
11. SUDECK, P.: Ueber die akute (trophoneurotische) Knochenatrophie nach Entzündungen und Traumen der Extremitäten, Deutsch. med. Wchnschr., 1902, xxviii, 336–338.
12. SUDECK, P.: Die Kollateralen Entzündungsreaktionen an den Gliedenassen (sog. akute Knochenatrophie), Arch. f. klin. Chir., 1938, cxci, 710–753.
13a. OSLER, W.: Lectures on angina pectoris and allied states, 1897, Appleton, N. Y., p. 50 (called to our attention by Max Trubek).
13b. HOWARD, T.: Cardiac pain and periarthritis of the shoulder, Med. Jr. and Rec., 1930, cxxxi, 364–365.
13c. SHAPIRO, E., LIPKIS, M. L., and KAHN, J.: "Trophic" ulcers of the hands complicating myocardial infarction, Am. Jr. Med. Sci., 1947, ccxiv, 288.
14. LIBMAN, E.: Symposium: angina pectoris with special reference to coronary artery disease, Bull. N. Y. Acad. Med., 1935, xi, 427.
15. EDEIKEN, J., and WOLFERTH, C. C.: Persistent pain in the shoulder region following myocardial infarction, Am. Jr. Med. Sci., 1936, cxci, 201–210.
16. BOAS, E. P., and LEVY, H.: Extracardiac determinants of the site and radiation of pain in angina pectoris with special reference to shoulder pain, Am. Heart Jr., 1937, xiv, 540–554.
17. LEECH, C. B.: Painful shoulder in association with coronary artery disease, Rhode Island Med. Jr., 1938, xxi, 104–106.
18. ERNSTENE, A. C., and KINELL, J.: Pains in the shoulder as a signal of myocardial infarction, Arch. Int. Med., 1940, lxvi, 800–806.
19. ASKEY, J. M.: The syndrome of painful disability of the shoulder and hand complicating coronary occlusion, Am. Heart Jr., 1941, xxii, 1–12.
20. JOHNSON, A. C.: Disabling changes in the hand resembling sclerodactylia following myocardial infarction, Ann. Int. Med., 1943, xix, 433–456.
21. DUPUYTREN, G.: De la retraction des doigts par suite d'une affection de l'aponeurose palmarie; operation chirurgicale qui convient dous ce cas, Jr. Univ. et hebd. de med. et chir. prat., 1832, 2.5, v, 348–365.
22. KANAVEL, A. B., KOCH, S. L., and MASON, M. L.: Dupuytren's contracture with a description of the palmar fascia, a review of the literature and a report of twenty-nine surgically treated cases, Surg., Gynec. and Obst., 1929, xlviii, 145–190.
23. MEYERDING, H. W., BLACK, J. R., and BRODERS, A. C.: The etiology and pathology of Dupuytren's contracture, Surg., Gynec. and Obst., 1941, lxxii, 582–590.
24. HORWITZ, T.: Dupuytren's contracture—a consideration of the anatomy of the fibrous structures of the hand in relation to this condition, with an interpretation of the histology, Arch. Surg., 1942, xliv, 687–706.
25. NIPPERT, A.: Konstitution, Stoffwechsel und Dupuytrensche Kontrakter, Deutsch. Ztschr. f. Chir., 1929, ccxvi, 289–292.
26. POWERS, H.: Dupuytren's contracture one hundred years after Dupuytren: interpretation, Jr. Neurol. and Ment. Dis., 1934, lxxx, 386–409.
27. Quoted by Kennard and Bucy.[29, 30]
28. GOWERS, W. R.: A manual of diseases of the nervous system, 1888, J. and A. Churchill, London, Vol. 2, p. 77.

29. KENNARD, M. A.: Vasomotor disturbances resulting from cortical lesions, Arch. Neurol. and Psychiat., 1935, lxxxiii, 537–545.
30. BUCY, P. C.: Vasomotor changes associated with paralysis of cerebral origin, Arch. Neurol. and Psychiat., 1935, xxxiii, 30–52.
31. LUHAN, J. A.: Hemiedema in cases of hemiplegia, Arch. Neurol. and Psychiat., 1936, xxxvi, 42–57.
32. ELLIS, L. B., and WEISS, S.: Vasomotor disturbances and edema associated with cerebral hemiplegia, Arch. Neurol. and Psychiat., 1936, xxxvi, 362–372.
33a. STEINBROCKER, O.: Painful homolateral disability of shoulder and hand with swelling and atrophy of hand, Ann. Rheum. Dis., 1947, vi, 80; The shoulder-hand syndrome, Am. Jr. Med., 1947, iii, 402.
33b. STEINBROCKER, O., SPITZER, N., and FRIEDMAN, H. H.: The shoulder-hand syndrome (reflex dystrophy of the upper extremity), Exhibit, Post-Grad. Medicine. (In press.)
34. BINGHAM, J. A. W.: Causalgia of the face: two cases successfully treated by sympathectomy, Brit. Med. Jr., 1947, i, 804–805.
35. EVANS, J. A.: Sympathectomy for reflex sympathetic dystrophy, Jr. Am. Med. Assoc., 1946, cxxxii, 620–623; Reflex sympathetic dystrophy: report on 57 cases, Ann. Int. Med., 1947, xxvi, 417–426.
36. MARQUES, S.: Herpes zoster e Osteodistrofia, Arq. brasil. de cir. e ortop., 1938, vi, 77–80.
37. OPPENHEIMER, A.: The swollen atrophic hand, Surg., Gynec. and Obst., 1938, lxvii, 446–454.
38. KELLY, M.: The nature of fibrositis. II. A study of the causation of the myalgic lesion (rheumatic, traumatic, infective), Ann. Rheumat. Dis., 1946, v, 69–77.
39. COLLINS, V. J., FOSTER, W. L., and WEST, W. J.: Vasomotor disturbances in poliomyelitis with special reference to treatment with paravertebral sympathetic block, New Eng. Jr. Med., 1947, ccxxxvi, 694–697.
40. KEHL, K. C.: Dupuytren's contracture as a signal to coronary artery disease and myocardial infarction, Ann. Int. Med., 1943, xix, 213–223.
41. SWEETAPPLE, H. A.: Sudeck's atrophy, Med. Jr. Australia, 1946, ii, 581–584.
42. WRIGHT, I. S.: The neurovascular syndrome produced by hyperabduction of the arms, Am. Heart Jr., 1945, xxix, 1.
43. TELFORD, E. D., and MOTTERSHEAD, S.: The "costoclavicular syndrome," British Med. Jr., 1947, 325.
FALCONER, M. A., and WEDELL, G.: The costoclavicular syndrome, Lancet, 1943, ii, 539.
44. DE GUTTIEREZ-MAHONEY, C. G.: The treatment of painful phantom limb by removal of post-central cortex, Jr. Neurosurg., 1946, i, 156.
45. WOLFF, JULIUS: Ueber einen Fall von Ellenbogensgelenks-Reaktion, Arch. f. klin. Chir., 1877, xx, 771–795.
46. WOLFF, JULIUS: Ueber trophische Störungen bei primaren Gelenksleiden, Berl. klin. Wchnschr., 1883, xx, 418, 422–426.
47. KÜMMELL, H.: Ueber die traumatischen Erkrankungen der Wirbelsäule, Deutsch. med. Wchnschr., 1895, xxi, 180–181.
48. KIENBÖCK, A.: Ueber Knochenveranderungen bei gonorrhoischer Arthritis und akute Knochenatrophie überhaupt, Wien. klin. Wchnschr., 1903, xvi, 57–63, 99–105.
49. LERICHE, R.: The surgery of pain, 1939, Williams and Wilkins, Baltimore.
50. FONTAINE, R., and HERMANN, L. G.: Post-traumatic painful osteoporosis, Ann. Surg., 1933, xcvii, 26–61.
51. GURD, F. B.: Post-traumatic acute bone atrophy—a clinical entity, Arch. Surg., 1936, xxxii, 273–291.
52. HERMANN, L. G., and CALDWELL, J. A.: Diagnosis and treatment of post-traumatic osteoporosis, Am. Jr. Surg., 1941, 511–630.

53. HERMANN, L. G., REINEKE, H. G., and CALDWELL, J. A.: Post-traumatic painful osteoporosis: a clinical and roentgenological entity, Am. Jr. Roent. and Rad. Ther., 1942, xlvii, 353–361.
54. WECHSLER, ISRAEL S.: A textbook of clinical neurology, 4th Ed., 1939, W. B. Saunders Company, Philadelphia, p. 366.
55. LORENTE DE NÓ, R.: Analysis of the activity of the chain of internuncial neurons, Jr. Neurophys., 1938, i, 207.
56. KEY, A. J., FISCHER, F., and ELZINGE, E.: Local atrophy of bone, Arch. Surg., 1934, xxviii, 936–947.
57. MUMFORD, E. B.: Roentgentherapy in acute osteoporosis—a new type of treatment, Jr. Bone and Joint Surg., 1938, xx, 949.
58. STEINBROCKER, O., SPITZER, N., and FRIEDMAN, H. H.: The treatment of the shoulder-hand syndrome (reflex dystrophy of the upper extremity), with special reference to sympathetic block, Anesthesia and Analgesia. In press.
59. FINDLAY, T., and PATZER, R.: The treatment of herpes zoster by paravertebral-procaine block, Jr. Am. Med. Assoc., 1945, cxxviii, 1217.
60. BERRY, R. L., CAMPBELL, K. N., LYONS, R. H., MOE, G. K., and SUTHER, M. R.: The use of tetraethylammonium in peripheral vascular disease and causalgic states, Surgery, 1946, xx, 525–535.

THE ACTION OF NEOSTIGMINE IN SUPRAVENTRICULAR TACHYCARDIAS *

By Samuel Waldman, M.D., and Louis Pelner, M.D.,
Brooklyn, New York

Neostigmine has been used successfully in the treatment of supraventricular tachycardias.[1, 2, 3, 4, 5, 6] Its action is predicated upon the cholinergic activity of this drug, which in these cases effects its often dramatic action through the vagus nerve. By inhibiting the action of cholinesterase at the myoneural junction, it permits the action of choline to exert its full effect. Study of the action of neostigmine in tachycardias has made it evident that its action is of somewhat specific value in treating sinus tachycardias, paroxysmal auricular tachycardias, and paroxysmal nodal tachycardias. By correcting the chemical and physical imbalance which has resulted in the accelerated heart rate, neostigmine exerts a definitive effect. Waldman and Moskowitz [1] first demonstrated its effectiveness in sinus tachycardia and in paroxysmal auricular tachycardia in 1941. These findings were soon confirmed by Pelner [2] who also felt that the carotid sinus was made more sensitive by neostigmine. In 1944, again, Waldman and Moskowitz showed excellent results in 18 cases of sinus tachycardia, not associated with organic disease. Recently [5] in studying the electrocardiographic effects of neostigmine it was found that the cardiac rate was slowed in 86 patients with all types of tachycardias including auricular fibrillation and auricular flutter. Our experience has not confirmed a slowing effect in auricular fibrillation and auricular flutter.

The Vagus Nerve and the Innervation of the Heart (Figure 1)

The left and right vagus nerves are cardio-inhibitory in action and carry fibers by way of the parasympathetic division of the autonomic nervous system from the cardio-inhibitory centers in the medulla to the supraventricular region of the heart. The cardiac vagal fibers separate from the main trunk, in the neck, between the origin of the superior and inferior laryngeal branches. The fibers then, in combination with the fibers of the accelerator nerves enter into the formation of the superficial and deep cardiac plexuses. Thence they go directly to the heart.

Fibers from the right nerve terminate around ganglion cells in auricular tissue in the region of the sino-auricular node. These cells serve as relay stations in the transmission of the vagal influence. Their axons enter the node and form a plexus around muscle cells in sino-auricular tissue. The left nerve enters into similar relationships with the auriculo-ventricular node.

* Read before the Eastern Section of the American Federation for Clinical Research at New York Hospital on December 12, 1947.

Its terminations arborize around ganglion cells in the inter-auricular septum which send axons to the muscular elements of the nodal tissue. Although the right nerve is chiefly distributed to the sino-auricular node and the left to the auriculo-ventricular node, each node receives some filaments from the opposite nerve.

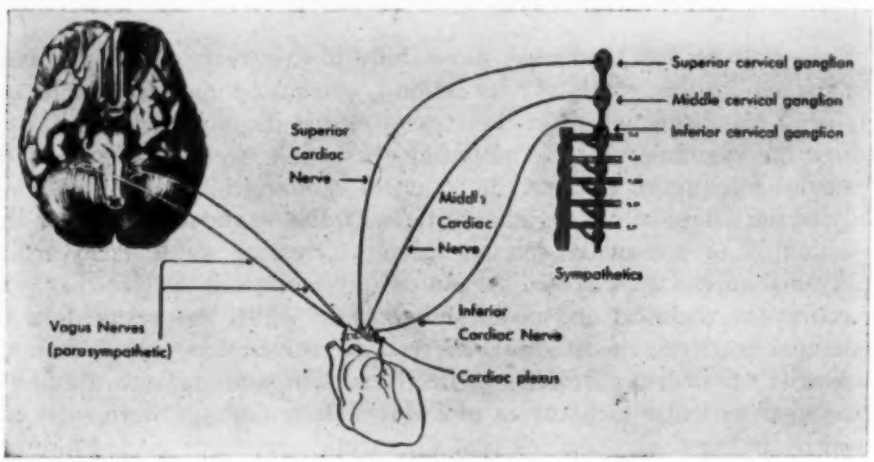

FIG. 1. Innervation of the heart.

Stimulation of the vagus nerve causes slowing of the heart mainly by the lengthening of diastole. Systole is little affected. The vagus exerts its effect on the heart by action on the auricular muscle, the sino-auricular node, and the auriculo-ventricular node. There is no direct action on the ventricular muscle. The ventricular slowing is secondary to auricular slowing, or stoppage, or to depression of auriculo-ventricular conduction (block). The right and left vagus nerves differ in their action. Stimulation of the right vagus nerve results mainly in slowing of the auricular beat and thus reduces the ventricular rate. Stimulation of the left nerve causes ventricular slowing by depressing auriculo-ventricular conduction and if strong enough may block auricular impulses.

From this anatomical discussion and from the knowledge of the physiologic action of neostigmine it becomes evident that the effect of neostigmine should be on the sino-auricular node, auricular muscle and auriculo-ventricular node. Apparently this is so, according to the studies described in this paper. It is believed that the basis of some cardiac disturbances is primarily chemical changes in heart muscle without histologic changes.[7] Raab [8] believes that some common forms of heart disease are due to biochemical changes in which the sympathomimetic amines play a dominant rôle. Katz et al.[9] also feel that cardiac arrhythmias may be dependent upon an imbalance of the autonomic nervous system or the endocrine system. Emotional disturbances may create imbalance in these systems. The tachy-

cardias are probably produced in the same way; and neostigmine, by correcting the imbalance through action on the vagus, restores the heart to normal rhythm.

In the case of sinus tachycardia, neostigmine decreases the rate of impulse formation at the sino-auricular node. This is evident by the increased TP interval (figures 2 and 3) due to the slower sino-auricular node impulse formation. This is effected through action of both vagi, predominantly the right which contacts the sino-auricular area where the biochemical change probably has occurred.

In paroxysmal auricular tachycardia, the ectopic focus is somewhere in the auricle, not in the sino-auricular node. Stimulation of the right vagus would slow the sinus rate but might not slow the rate of impulse formation issuing from an ectopic focus in the auricle. However, stimulation of the left vagus could slow the ventricular rate by decreasing conductivity at the auriculo-ventricular node and thus produce a block of some degree. This actually takes place (cases 3 and 4, figures 4 and 5).

In paroxysmal nodal tachycardia, again, the left vagus effect would be expected to be the predominant factor for the same reason. That this occurs is again shown by electrocardiographic studies (case 5 and figure 6).

We thus see that a selective predominant vagus stimulating effect, as would be theoretically suggested, actually takes place and by this means supraventricular tachycardias are corrected by the action of neostigmine. In sinus tachycardias, it slows impulse formation at the sino-auricular node; in paroxysmal auricular and nodal tachycardias it creates a degree of block in the auriculo-ventricular bundle and soon normal rhythm is reëstablished.

In the present study, the same methods were used as were previously employed.[1, 4] An initial complete electrocardiogram was taken. Then the injection of 1 mg. neostigmine methylsulfate was given and tracings were taken every five minutes in Lead II for 20 minutes. It was found before that the full effect is evident within 20 minutes, or not at all. Goldfinger and Wosika[5] also found 20 minutes the optimal time for response.

Illustrative Cases

Sinus Tachycardias

Case 1. S. F., female, aged 36, married, was seen during an attack of sinus tachycardia, complaining of severe palpitation and pain in the left chest. The past history was irrelevant except for the family history. Her father had died two years before, following a second attack of myocardial infarction due to coronary occlusion. Her mother has severe hypertension. The patient was quite emotional and with this family history was quite cardio-sensitive so that emotional disturbances focused on the heart. This is not an uncommon condition.[9]

Physical examination, fluoroscopy and electrocardiogram (figure 2A, B, C, D) of the patient revealed no evidence of heart disease. The pulse rate during the attack varied from 115 to 125, the blood pressure was 160 mm. Hg systolic and 90 mm. diastolic.

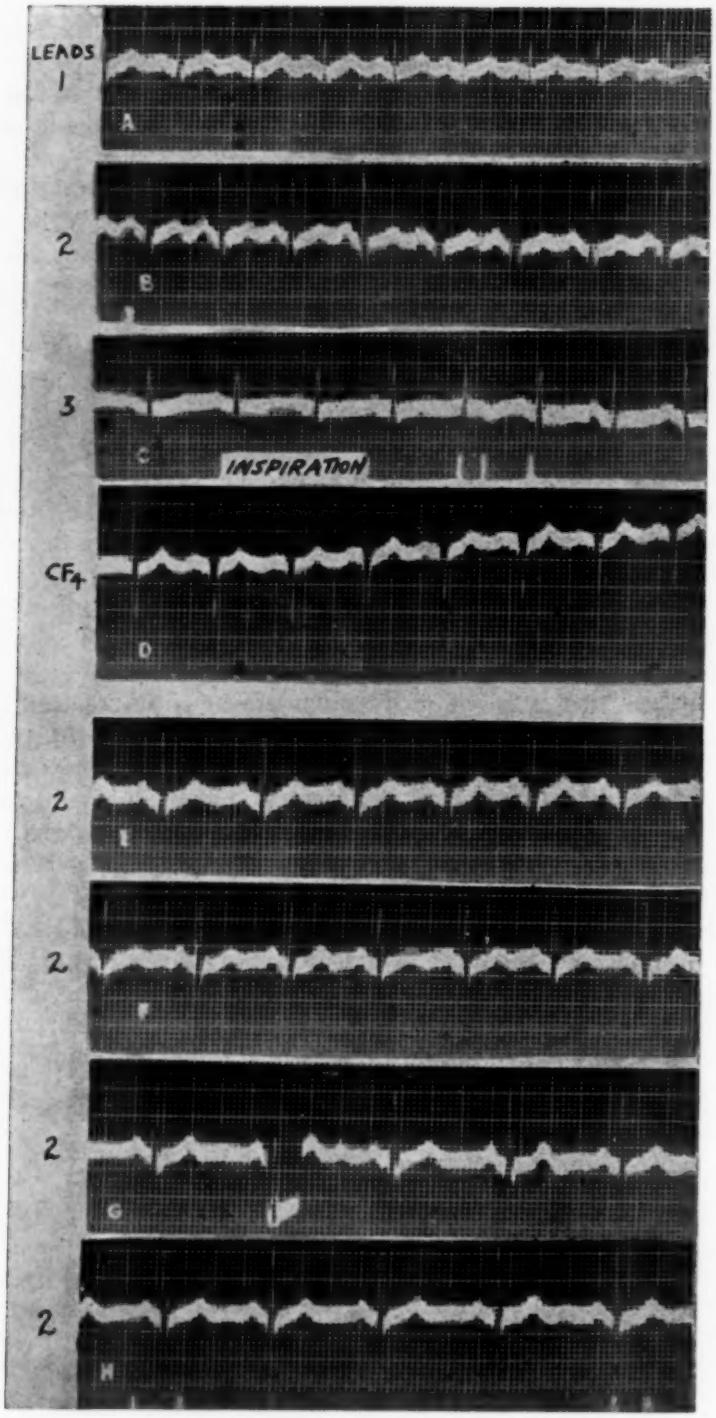

FIG. 2. *Case 1.*

S. F., female, no organic heart disease. A, B, C, D—standard and precordial leads showing a sinus tachycardia of 115 to 125 before the injection of 1 mg. neostigmine. E—five minutes after injection of 1 mg. neostigmine methylsulfate, rate is reduced to 96. F—10 minutes after the injection, rate is still 96. G—15 minutes after the injection the rate is 79. H—20 minutes after the injection the rate is 75.

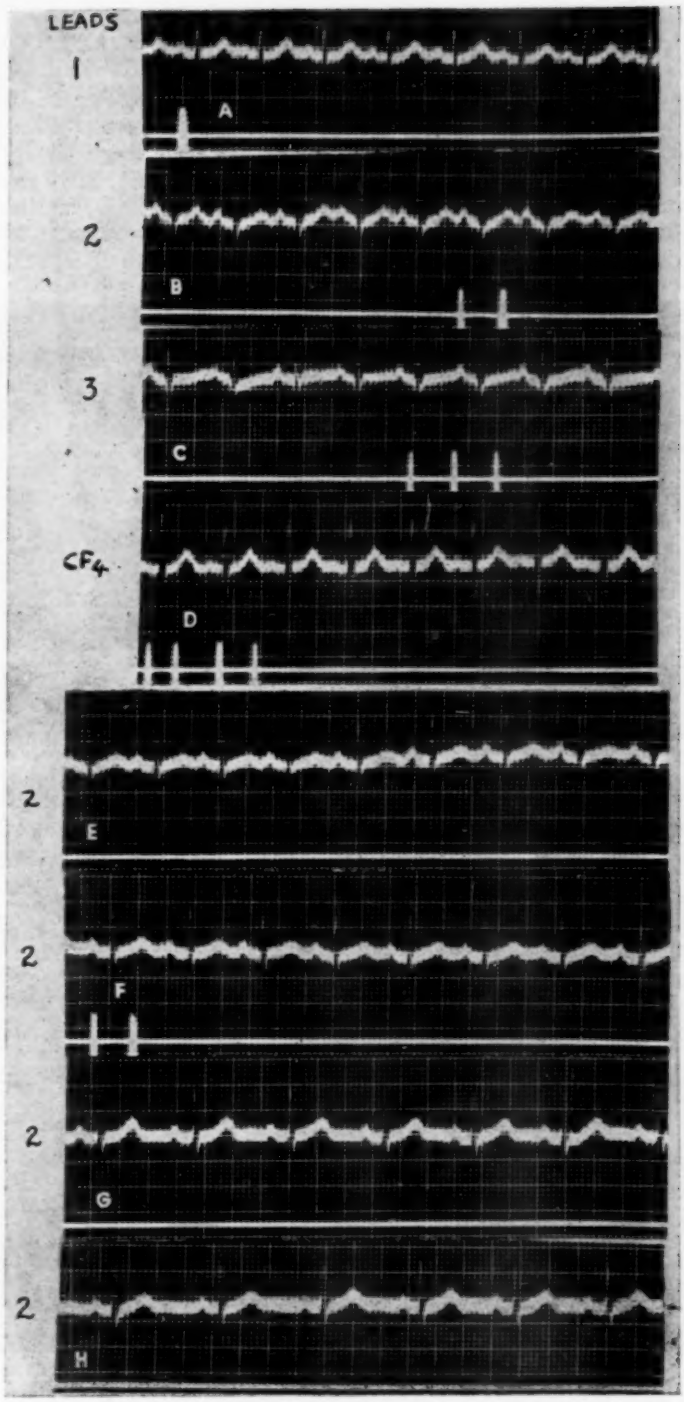

FIG. 3. *Case 2.*

R. G., female, no organic heart disease. A, B, C, D—standard and precordial leads showing attack of sinus tachycardia. Rate is 136. E—five minutes after injection of 1 mg. neostigmine methylsulfate rate slowed to 115. F—10 minutes after the injection, the rate is 107. G—15 minutes after injection the rate is 88. H—20 minutes after injection the rate is 83.

The patient was given an injection of 2 c.c. of neostigmine methylsulfate (1:2000 = 1 mg.) intramuscularly, and electrocardiograms were taken at five minute intervals for the next 20 minutes using Lead II as the recording lead.

Within five minutes the rate had slowed to 96 (figure 2E), in 10 minutes it was still 96 (figure 2F), in 15 minutes the rate was 79 (figure 2G), and in 20 minutes it was 75 (figure 2H). The patient felt much better, and was relieved of her anxiety and palpitation.

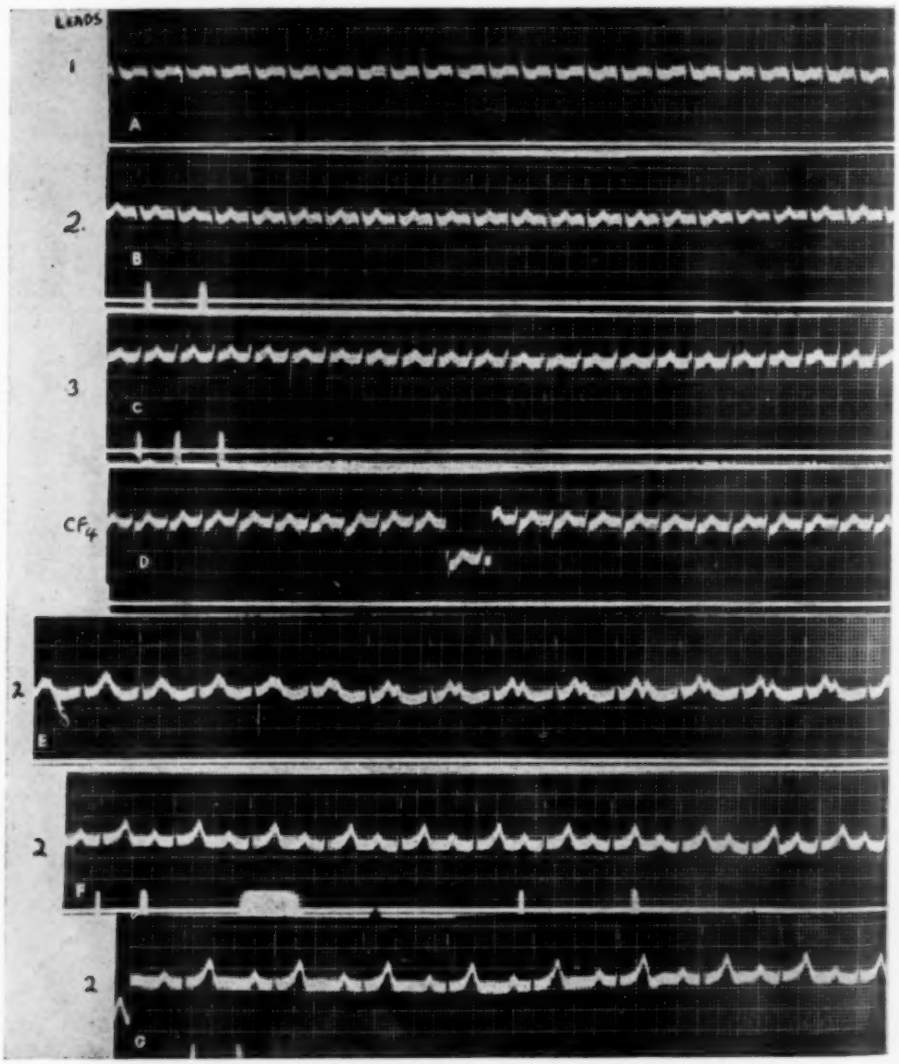

FIG. 4. *Case 3.*

L. F., female, rheumatic heart disease. A, B, C, D—standard and precordial leads exhibit a paroxysmal auricular tachycardia at the regular rate of 166. E—five minutes after injection of 1 mg. neostigmine the ventricular rate slowed to 94 to 100, and PR interval was 0.36 second (first degree heart block). F—In 10 minutes the rate varies from 79 to 88 with PR interval of 0.24 second. G—after 15 minutes the rate is 71 and the PR interval is 0.22 second.

Case 2. R. G., female, aged 27, married, noted recent frequent attacks of palpitation associated with nervousness. These were increasing in severity and duration and caused insomnia and anorexia, associated with fretfulness. She appeared in the office with a pulse rate of 136, blood pressure 154/80. Physical and fluoroscopic examination revealed no evidence of organic heart disease. She was extremely agitated. Carotid sinus pressure caused only temporary slowing of the heart. Reassurance was of no avail. An injection of 1 mg. neostigmine methylsulfate was given intramus-

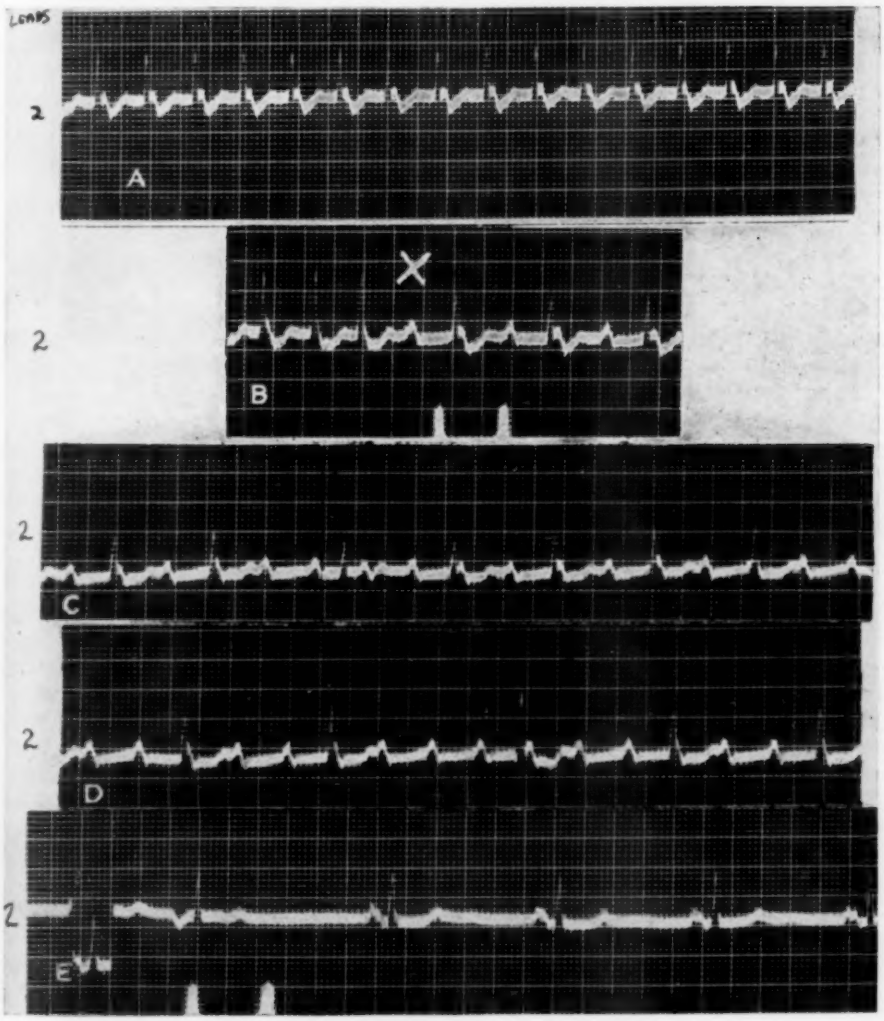

FIG. 5. *Case 4.*

R. R., 47, female, with long-standing rheumatic heart disease. Figures are of Lead II. A—before injection—paroxysmal auricular tachycardia with a rate of 188. B—3 minutes after injection of 1 mg. neostigmine the auricular rate is 188, ventricular rate is 94. "X" marks onset of 2:1 block. C—8 minutes after injection, varying 3:1, 2:1 block is present. D—33 minutes after injection, varying 3:1 to 4:1 block is present. Auricular rate is 188, ventricular rate averages 60. E—sinus bradycardia (56) 2 days later, auricular premature contraction present. (Reprinted from Medical Record, 1941, cliii, 134.)

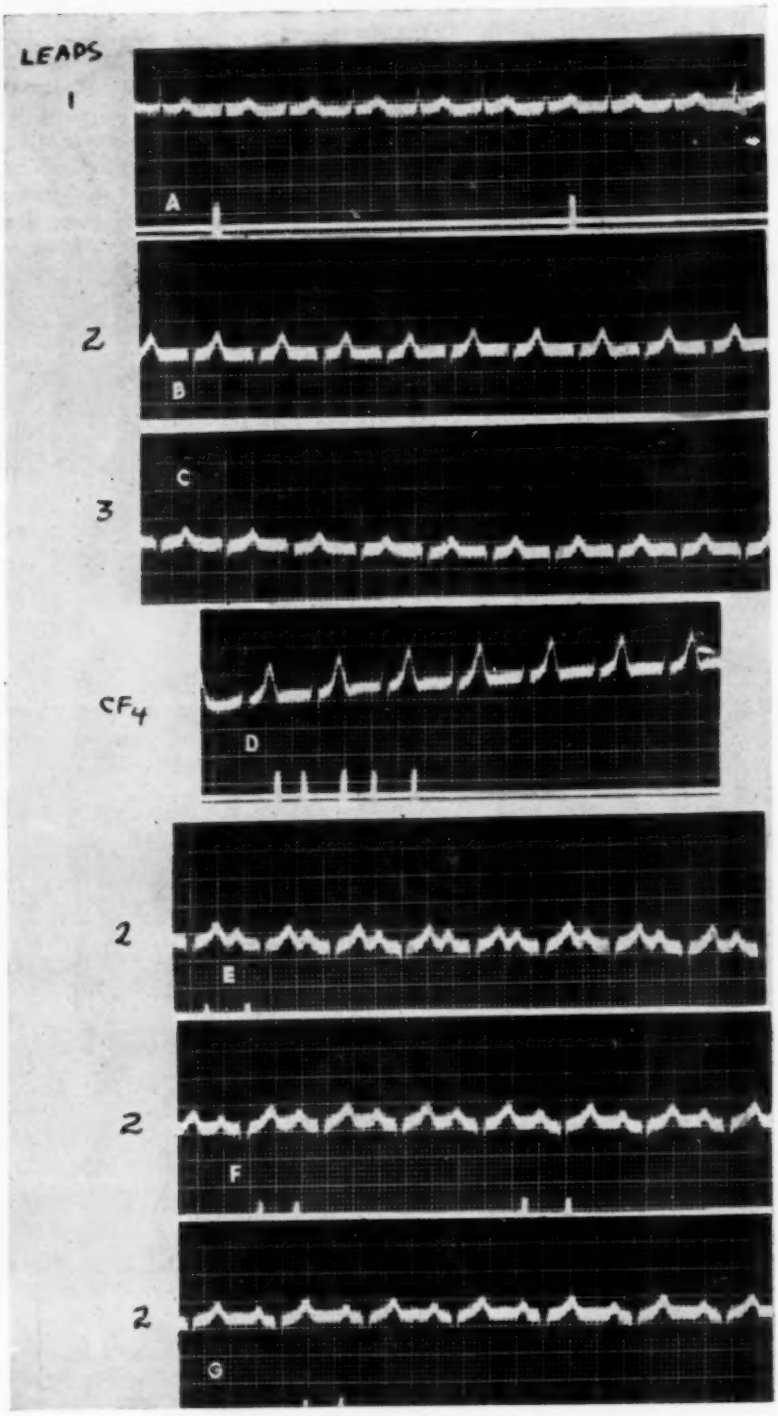

FIG. 6. *Case 5.*

F. A., female, rheumatic heart disease. A, B, C, D—standard and precordial leads show a nodal tachycardia, rate 136. E—five minutes after injection of 1 mg. neostigmine methylsulfate the rate has dropped to 115, PR interval 0.21 second. F—10 minutes later the rate is 100, PR interval 0.18 second. G—15 minutes later the rate is 88. PR is 0.16 second.

cularly. The electrocardiogram before injection is seen in figure 3 A, B, C, D, the rate being 136. In five minutes the rate slowed to 115 (figure 3 E), in 10 minutes to 107 (figure 3 F), in 15 minutes to 88 (figure 3 G), and in 20 minutes to 83 (figure 3 H). Following this response, the patient felt much better and became receptive to reassurance as to the benign nature of the attacks. Further attacks then were minimal, created less disturbance to the patient, and finally attacks failed to recur.

From the electrocardiographic studies in these cases, it is evident that the slowing of the heart rate was dependent upon a decrease in the rate of impulse formation at the sino-auricular node. This is apparent by the increase in the TP interval. Neostigmine, therefore, in these instances, produced the slowing effect by stimulation of the vagus nerve (especially the right) which has its terminations mainly at the sino-auricular node, where the rate of impulse formation was excessively rapid. Probably by correcting a chemical imbalance, restoration of a normal rate was established.

Paroxysmal Auricular Tachycardia

Case 3. L. F., 20 years old, married, female, was a known rheumatic cardiac with mitral stenosis and insufficiency and aortic stenosis and insufficiency. She had been having frequent recurrent attacks of palpitation which at times would last several days.

When seen at the office, she had a rapid regular tachycardia of 166 beats per minute. The electrocardiogram (figure 4A, B, C, D) showed a typical paroxysmal auricular tachycardia. Carotid sinus and ocular pressure were of no avail. One milligram of neostigmine was given intramuscularly. In five minutes, the tachycardia had slowed to 94–100. The electrocardiogram (figure 4E) showed a P-wave appearing on a T-wave and then breaking away into an individual P-wave. The PR interval during this change was 0.36 second (first degree auriculo-ventricular block). In 10 minutes the rate of the heart varied from 79 to 88 and the PR interval measured 0.24 second (figure 4F). In 15 minutes the rate was 71 (normal sinus rhythm) and the PR interval was 0.22 second (figure 4G).

This patient is still under the medical care of one of us (S. W.). Because of the frequently recurring attacks, attempts at prevention were made. Digitalization failed to prevent the attacks. Quinidine diminished their frequency. Since neostigmine injection repeatedly aborted the attacks and since previous experience [4] showed that oral medication helped some cases, the latter therapy was attempted. The patient was given neostigmine bromide, 0.015 gm., three times daily at equal intervals. Since October, 1945 when this regime was begun, she has had only a few, short lasting attacks. No attack was severe enough to require any additional medication, oral or parenteral. The patient volunteered the information that neostigmine bromide helped her more than quinidine or digitalis and she continues to take the neostigmine tablets despite the relatively higher cost.

In this case the neostigmine induced a heart block by vagal stimulation causing auriculo-ventricular block of first degree. Following this, the rhythm became normal.

Case 4. [This case has previously been reported [1] but is being used here to demonstrate another form of auriculo-ventricular block produced by neostigmine.]

R. R., female, single, aged 47, had rheumatic heart disease of 25 years' duration with mitral stenosis and insufficiency. She had had frequent attacks of tachycardia

which unnerved her despite her knowledge of their nature. The attack shown here occurred on July 27, 1940 and had lasted eight hours when the patient was seen. The rate was 188 beats per minute and the electrocardiogram demonstrated a paroxysmal auricular tachycardia (figure 5A). Other methods (digitalis, quinidine in maintenance doses, carotid sinus and eyeball pressure), having failed to prevent or terminate the attacks, one milligram of neostigmine methylsulfate was injected intramuscularly. In three minutes the ventricular rate dropped to 94, while the auricular rate persisted at 188; a 2:1 heart block had developed (figure 5B). There was marked relief with alleviation of the cyanosis which had been present. Five minutes later there was a 3:1, 2:1 block (figure 5C). For 33 minutes (figure 5D) the cardiac rhythm persisted with a block varying from 3:1 to 4:1. The auricular rate remained at 188, while the average ventricular rate dropped to 60. A graph taken two days later revealed a sinus bradycardia, rate 56, with occasional auricular premature contraction (figure 5E). It may also be noted that the P-waves were peaked during the period of block when they became easily visible, while they were low, wide and notched in the interval graph. This indicated an ectopic origin of the P-wave during the tachycardia, which is expected in paroxysmal auricular tachycardia. This patient had other similar episodes which responded, similarly with heart block, to injections of neostigmine methylsulfate.[1]

In this instance the cessation of the attack of paroxysmal auricular tachycardia was secondary to the induction of partial heart block by neostigmine. The heart block was of second degree with varying 2:1, 3:1 and 4:1 incomplete auriculo-ventricular block. We thus see that the neostigmine again was effective through vagal action, especially affecting the left vagus (which terminates mostly at the auriculo-ventricular bundle), and by producing the block corrects the imbalance and thus permits the resumption of normal sinus rhythm.

Paroxysmal Nodal Tachycardia

Case 5. F. A., female, unmarried, age 22, had recurrent attacks of palpitation for the past two or three years. She was a known rheumatic cardiac with mitral stenosis and insufficiency. On the day the study was made, she had noted palpitation for the preceding five hours and could not relieve it with sedatives, rest and ice bags. At the onset of the test the pulse rate was 136 per minute. The electrocardiogram (figure 6A, B, C, D) showed a nodal (probably mid-nodal) tachycardia with a rate of 136 per minute. An injection of 1 mg. of neostigmine was given. In five minutes the rate dropped to 115 (figure 6E). A P-wave appeared with a PR interval of 0.21 second. A slight degree of first degree block was produced. In 10 minutes the rate was 100 and PR interval was 0.18 (figure 6F). In 15 minutes the rate was 88 with PR interval 0.16 second (figure 6G).

It is here apparent that the neostigmine effected its action through the vagus, on the auriculo-ventricular bundle. Here it produced a slight degree of block; and the sino-auricular node took over impulse formation. Within 15 minutes the block disappeared and normal sinus rhythm returned.

Summary

The anatomical and physiological relations of the vagus nerve and the action of neostigmine are discussed. In sinus tachycardia neostigmine re-

duces the rate by slowing impulse formation at the sino-auricular node through stimulation of the vagus, especially the right. In paroxysmal auricular and nodal tachycardias, it slows the heart rate by stimulating the vagus, especially the left, thus inducing incomplete heart blocks of varying degree. Five cases are presented to demonstrate this action of neostigmine methylsulfate in the treatment of supraventricular tachycardias.

Comment

From this study it appears that neostigmine exerts a somewhat selective specific effect on supraventricular tachycardias, depending upon the site of origin. It exerts this action through the medium of vagal stimulation. It seems that this action adds credence to the currently growing concept that many functional and some organic disorders of the heart are of metabolic, or chemical origin secondary to disturbances in the autonomic and/or endocrine systems.

Part of the supplies used in this study was furnished through the courtesy of Messrs. Freeman and Handsman of Hoffmann-LaRoche, Inc., Nutley, N. J.

BIBLIOGRAPHY

1. Waldman, S., and Moskowitz, S. N.: The effect of prostigmin on supraventricular tachycardias, Med. Rec., 1941, cliii, 134.
2. Pelner, L.: Prostigmin in paroxysmal tachycardia, Med. Rec., 1941, cliii, 209.
3. Battro, A., Segura, R. G., and Lanari, A.: El prostigmin en el tratamiento de las taquicardias paroxisticas supraventriculares, Medicina, 1941, i, 4.
4. Waldman, S., and Moskowitz, S. N.: The treatment of attacks of sinus tachycardia with prostigmin, Ann. Int. Med., 1944, xx, 793.
5. Goldfinger, D., and Wosika, P. H.: The electrocardiographic effects of prostigmin, Am. Jr. Med. Sci., 1946, ccxii, 418.
6. Bellet, S.: Diagnosis and treatment of cardiac arrhythmias, Med. Clin. N. Am., 1946, 1307.
7. Pallares, E. S., Orozco, F. V., and Riviero, J. M.: Note on a pentose isolated from heart muscle, Am. Heart Jr., 1947, xxxiii, 705.
8. Raab, W.: Sympathomimetic amines in the heart muscle; their pathogenic and therapeutic significance, Am. Heart Jr., 1947, xxxiii, 707.
9. Katz, L. N., Winton, S. S., and Megibow, R. S.: Psychosomatic aspects of cardiac arrhythmias; a physiological dynamic approach, Ann. Int. Med., 1947, xxxi, 261.

OBSERVATIONS ON THE USE OF THE RESPIRATOR IN REFRACTORY STATUS ASTHMATICUS *

By Morton F. Reiser, M.D., and Eugene B. Ferris, Jr., M.D., F.A.C.P.,
Cincinnati, Ohio

Introduction

Recent advances in our knowledge of the nature and management of bronchial asthma have contributed greatly to the intelligent handling and well being of patients afflicted with this disorder. Interim treatment oriented in relation to allergic,[1] psychiatric,[2] and physiologic [3] considerations has greatly increased the comfort of asthma sufferers, and has reduced the frequency of acute episodes of asthmatic breathing. For the acute attack the physician now has at his disposal a powerful armamentarium of antispasmodic and sedative drugs in addition to materials for effective inhalation therapy; yet a small number of patients suffering status asthmaticus fail to respond to the most heroic and carefully planned therapy available. It is the purpose of this communication to present a new therapeutic maneuver (use of the Drinker Respirator) which appears to be of value in the treatment of such cases.

Rationale and Pathological Physiology

The rationale of this therapeutic maneuver is based upon a consideration of the pathological physiology of asthma. In the obstructive dyspnea of asthma there is greater interference with expiration than with inspiration. This is suggested clinically by the prolongation of the act of expiration and the occurrence of wheezes and other signs of tubular narrowing primarily in the expiratory phase of respiration. In chronic asthma, the chest gradually expands and assumes more and more a position of deep inspiration, as chronic emphysema with its limitation of the range of respiratory excursion develops. In cases of acute intractable asthma (status asthmaticus) one can watch the development of acute emphysema with the chest expanding progressively with each inspiration, as the expiratory phase becomes increasingly more ineffective.

There seem to be several factors underlying this phenomenon of acute ballooning of the lungs. It should be remembered that normally inspiration is an active process, whereas expiration is passive, the air flowing outward because of the elastic recoil of the lungs and the diminution in chest volume attendant to relaxation of the diaphragms and inspiratory muscles. The only muscles that can play an active rôle in expiration are those of the ab-

* Received for publication September 20, 1947.
From the Department of Internal Medicine, University of Cincinnati College of Medicine

dominal wall and the internal intercostals.[4] With obstruction during the inspiratory phase (as exists in the diffuse constant bronchiolar spasm of asthma), inspiration becomes more forcible resulting in a negative intrathoracic pressure greater than normal,[5, 6] and air is able to pass into the alveoli through the constricted bronchioles. The constricted passageway, however, is more effective in blocking the outflow of air during expiration. Considering the difference in physiologic rôles, it is likely that the accessory muscles of expiration are less efficient and more fatigable than those of inspiration. Further, the elastic recoil of the lungs during expiration normally permits bronchial narrowing during this phase, and it has been noted during bronchoscopic examinations that the degree of narrowing is greater than normal in patients with asthma.[3] As a result of the lagging expiratory efficiency, with each breath more air is drawn into the alveoli than can be expelled and the lungs become literally "blown up."

When the bronchial constriction cannot be adequately lessened by means of antispasmodic and/or sedative and anesthetic measures, the primary therapeutic aim must be the maintenance of adequate oxygenation until relief of the respiratory obstruction can finally be achieved, or until spontaneous remission occurs. The use of 100 per cent oxygen or 80 per cent helium—20 per cent oxygen will often relieve the cyanosis (anoxemia). In cases that do not respond to these measures, pressure breathing has been advocated as a helpful therapeutic measure. It serves to increase slightly the oxygen tension of the inspired air, to combat pulmonary edema, to maintain a more patent lumen during the expiratory phase, and to decrease inspiratory dyspnea. But in status asthmaticus, where the primary difficulty is in expiration (the chest and lungs being already maximally expanded), it would seem that the use of pressure breathing would serve to further the ballooning of the lungs and chest without correcting the main difficulty. Any of these technics of inhalation therapy will temporarily aid in the effectiveness of breathing and lessen the cyanosis. With intractable bronchial spasm this is accomplished largely by virtue of the active respiratory effort of the patient. The ability to maintain such an expenditure of energy in the face of prolonged anoxemia is obviously limited, and a point is eventually reached where the voluntary musculature becomes quite ineffectual and vital tissues such as the cardiac muscle and brain are dangerously embarrassed by the ever increasing degree of anoxemia. Unless oxygenation can be restored, collapse supervenes and death ensues rapidly.

Since expiration is primarily limited in asthma it would appear that the best procedure for the maintenance of adequate ventilation would be to support this phase. This can be effectively accomplished by the use of the Drinker Respirator which applies positive pressure to the chest wall and abdomen. Since the Respirator also aids inspiration, inspiratory dyspnea is at the same time decreased.

Case Reports

Case 1. R. R., a 45 year old colored female, was brought to the Cincinnati General Hospital in a moribund state on August 19, 1945 at 3 p.m.

The daughter revealed that the patient had been suffering from asthmatic attacks for 8 to 10 years. These episodes had occurred every two to four weeks up until the month prior to admission when they had increased in frequency, and had been occurring every two or three days. Previous attacks had been relieved by adrenalin or by a patent "asthma medicine." The present attack had started about 20 hours before admission to the hospital. Despite the usual medication and two "arm shots" given by her local physician, the patient had become progressively worse and had apparently lost consciousness about five hours before entering the hospital.

On admission the patient was unconscious, deeply cyanotic and in shock. The respirations were feeble and gasping and the respiratory rate was 10 per minute. All the accessory muscles of respiration were in use and the chest position was one of maximal inspiration. The entire chest was hyperresonant. Auscultation revealed only an occasional wheeze, breath sounds were inaudible, and respiratory exchange appeared to be extremely slight. The temperature was 102° F. The pupils were 3 mm. in diameter and did not react to light. The heart sounds were distant and irregular and the pulse was weak. The heart rate was 160 per minute, and the blood pressure was 70/40 mm. Hg. The tendon reflexes were normal throughout; there was no response to plantar stimulation.

Throughout the first 5½ hours of hospitalization 100 per cent oxygen was administered by mask, and the patient was given repeated doses of epinephrine and aminophylline intravenously and intramuscularly, without effect. Two doses of rectal ether were ineffectual. Parenteral fluids were administered intravenously. During the third hour the patient developed paroxysms of fine muscular twitching in the extremities, trunk, and face. The muscular twitching became more marked and at the end of five and one-half hours became convulsive in nature. Respirations were completely ineffectual, and the patient was deeply cyanotic and in shock. The pulse was feeble and irregular.

At this time the patient was placed in a Drinker Respirator. The cyanosis promptly disappeared, the pulse became of good quality, the heart rate fell to 120 per minute and the blood pressure rose. A 20 per cent oxygen–80 per cent helium mixture was substituted intermittently for oxygen. The muscular twitching disappeared. Administration of parenteral fluids (glucose and plasma) was continued. The patient was kept in the Respirator for six hours, and when the Respirator was turned off the patient was able to breathe satisfactorily at a rate of 28 per minute. The breath sounds could now be heard, the expiratory phase being prolonged. There was no wheezing. A few inspiratory râles were heard at both lung bases. Pulse and blood pressure were satisfactory. However, the patient had meanwhile developed a flaccid paralysis of all extremities and tendon reflexes were absent. Despite relief of the respiratory difficulty, the pulse gradually weakened and the blood pressure again fell. The patient was returned to the Drinker Respirator one and one-half hours later but failed to respond to this or to supportive therapy including coramine, caffeine, and plasma, and she died 14 hours after admission. At no time did she regain consciousness.

Comment. This patient had been dyspneic for almost a day and was unconscious during the five hours immediately preceding admission. When first examined she showed unmistakable signs of cerebral anoxia, and there followed gradual progression to the point of generalized convulsive mani-

festations before adequate oxygenation was established. The use of the Drinker Respirator afforded immediate and dramatic relief of the anoxemia as evidenced by the disappearance of cyanosis, the improvement in circulation, and the termination of convulsive phenomena. Although the asthma had undergone practically complete remission several hours before death, the patient failed to regain consciousness and there was further progression of the neurological findings. It would appear likely that her death was a direct result of prolonged cerebral anoxia which had initiated irreversible brain damage before adequate therapy could be instituted.

Case 2. W. B., a 47 year old white male, was admitted to the Cincinnati General Hospital on March 6, 1946 in a severe attack of acute asthmatic breathing of one hour's duration. His past history revealed onset of bronchial asthma in February 1944. In the following two years he had been seen in the receiving ward on 20 occasions for relief of acute attacks. The duration and frequency of the attacks had steadily increased and the amounts of antispasmodic, sedative, and oxygen therapy necessary for their relief had progressively increased. During this time he had been attending the out-patient dispensary where dental and paranasal foci of infection had been satisfactorily treated; routine medical care had been administered, and desensitization to house dust (the principal allergen revealed by skin testing) had been in progress since June 1944.

On admission the patient was apprehensive and panic striken. He was deeply cyanotic, his skin was cold, and he was drenched with perspiration. The chest was hyperresonant and fixed in a position of maximum inspiration, with all of the accessory muscles of respiration in use. Respiratory exchange was shallow; loud inspiratory and prolonged expiratory wheezes and rhonchi were heard over the entire chest. The blood pressure was 140 mm. Hg systolic and 100 diastolic and the pulse rate was 120 per minute. The remainder of the physical examination revealed nothing of note.

Oxygen, 100 per cent, by mask, intravenous aminophylline, subcutaneous epinephrine and sodium luminal failed to produce any improvement. After an hour and a half rectal ether was administered, an 80 per cent helium–20 per cent oxygen mixture was substituted for 100 per cent oxygen, and sodium iodide was given by intravenous route. For a while the patient seemed to benefit in that cyanosis was minimal, he seemed more relaxed, and the skin became warmer and less moist; but physical examination failed to reveal any evidence of relaxation of the bronchial spasm. He lost strength rapidly and five hours after admission he was again deeply cyanotic and covered with a cold sweat. Pulmonary ventilation seemed reduced almost to zero and the pulse rate rose to 140 per minute. Collapse seemed imminent. Coramine was given by vein and the patient was placed in a Drinker Respirator.

Improvement was immediate and dramatic. The patient appeared relaxed and comfortable and fell into a restful sleep. His skin became warm and dry and the cyanosis disappeared. The pulse stabilized at 120 per minute and was of good quality. Helium-oxygen mixture was continued throughout by mask and adrenalin in oil was administered at the end of the first hour in the Respirator. The patient remained in the Respirator for nine hours at the end of which time he awakened and was able to breathe adequately without its aid.

Examination now revealed evidence of only a very slight residual amount of respiratory obstruction. Subsequent recovery was uneventful. The patient was discharged from the hospital on March 9, 1946.

Case 3. L. G., a 46 year old white male, was brought to the Cincinnati General Hospital in profound shock on October 2, 1946 at 1:59 a.m. History revealed that

the patient had been suffering from asthma for six years. Attacks had been occurring more frequently during the preceding months, and for the five days prior to admission the patient had been unable to sleep at all because of difficult breathing. He had been using an adrenalin spray with some relief but on September 30, 1946 he had been obliged to call his local physician who administered adrenalin in oil and penicillin. Adrenalin in oil was given twice the following day (October 1) but dyspnea became progressively worse and patient was brought to the hospital early the next morning.

On admission the patient was cyanotic with cold clammy skin, unobtainable blood pressure, and a pulse rate of 150 per minute. The chest was emphysematous and fixed in the position of maximum inspiration. He was extremely apprehensive and restless; respirations were rapid (42 per minute) and extremely shallow. The breath sounds were almost inaudible on auscultation. The neck veins were distended; there was no peripheral edema. The temperature was 97° F. The white blood count was 17,500 white cells per cu. mm. with 85 per cent polymorphonuclear leukocytes and 15 per cent lymphocytes.

For the first five hour period 100 per cent oxygen was administered by mask. During this time the patient was given repeated intravenous injections of aminophylline, two six ounce doses of rectal ether, sodium iodide intravenously, epinephrine by subcutaneous injection, physiologic saline solution and plasma by vein, plus 100 mg. of Demerol and 4 grains of sodium amytal intramuscularly. Despite the therapy listed above no improvement was noted in the breathing or cyanosis, and the patient continued to be very restless and anxious. The blood pressure was still unobtainable.

At 7:00 a.m. an endotracheal tube was inserted and an 80 per cent helium–20 per cent oxygen mixture was substituted for 100 per cent oxygen, without effect. The temperature rose abruptly to 100° (rectal). Penicillin, 20,000 units, was injected intramuscularly and repeated every three hours thereafter. At 9:00 a.m. (seven hours after admission) the patient was placed in the Drinker Respirator. An additional 7½ grains of sodium amytal (intramuscularly) was required to quiet the patient sufficiently to allow for synchronization of his respirations with the rhythm of the Respirator. As soon as this had been accomplished there was dramatic disappearance of the cyanosis and recovery from the state of shock. The blood pressure was obtainable at 125/70 mm. Hg and the pulse slowed to a rate ranging between 90 and 120 per minute. For the first six hours in the Respirator this improvement in the patient's condition was maintained. Expiration remained prolonged but the breath sounds were clearly audible and the wheezes disappeared. Circulation remained adequate, and the color of the skin and mucous membranes indicated satisfactory oxygenation. During this period the patient received additional parenteral fluids, sedation as needed, and frequent intravenous injections of epinephrine.

At 4:00 p.m. temperature rose to 106.2° (rectal) and moderate cyanosis reappeared. Numerous fine inspiratory râles, rhonchi and occasional expiratory wheezes could be heard in the chest. Subsequently, his course was rapidly and progressively downward. At no time was he able to breathe adequately without the support of the Respirator, although bronchial spasm seemed minimal on physical examination. Twenty-two hours after admission the patient died.

Comment. The development of high fever, râles, and polymorphonuclear leukocytosis in this case is felt to indicate the presence of a complicating bronchopneumonia. The patient had suffered from prolonged respiratory distress for five days before admission to the hospital, and for the last two days of this period he had been severely dyspneic. Nevertheless, under treatment with the Drinker Respirator, there was prompt and main-

tained relief of the anoxemia, shock, and obstructive dyspnea before pneumonia altered the course of events.

Discussion

In all three cases under consideration the specific and directed application of mechanical energy for the support of expiration appears to have furnished the necessary crutch for maintenance of adequate respiratory exchange until the bronchial spasm had undergone remission. Disappearance of cyanosis was prompt and dramatic in each of these patients. In addition, improvement in the circulation attendant on the relief of anoxia is evident in each of the records. The recovery from shock in Case 3 after establishment of adequate oxygenation is particularly notable, and emphasizes the important rôle of oxygen in the treatment of shock. The unfavorable outcomes in Cases 1 and 3 can be explained on the basis of complicating factors, and need not be regarded as indicating failure of the therapy under consideration. The second patient was treated early in the course of his attack and recovered uneventfully. It is quite possible that if therapy could have been instituted earlier in Cases 1 and 3 the final outcomes would have been more favorable.

Comment

It is at once apparent that the induction of partial anesthesia is an integral part of the treatment. A patient in acute respiratory distress, being anxious and fearful to the point of panic, will attempt to fight the machine and be made worse unless the level of consciousness is sufficiently depressed to permit passive acceptance of the mechanical aid. Eighty per cent to 90 per cent synchrony of the excursions of the machine with the patient's respirations will provide adequate oxygenation. Adjustments in the rate or the pressure, or both, may be required as the treatment progresses.

Summary and Conclusions

The use of anesthesia plus the Drinker Respirator for artificial respiration, with active support of expiration, is suggested as an additional tool in the armamentarium of therapy for acute status asthmaticus. The pathological physiology of acute intractable asthma is discussed in relation to the rationale of this form of treatment. Three cases treated in this manner are presented and in each, prompt and satisfactory relief of anoxemia was accomplished and maintained until bronchiolar spasm had undergone remission. While it is admittedly impossible to draw any conclusions from limited experience such as this, we feel that the rationale is sufficiently clear and the results insofar as relief of anoxemia is concerned, are gratifying enough to warrant its use in refractory status asthmaticus. From our experience it is felt that it is of utmost importance that the therapy be instituted early in the course, before irreversible changes have appeared, or other grave

complications have had time to gain foothold. This maneuver is not suggested as a substitute for other well-established methods of treatment, but rather as an adjunct to them in refractory cases.

BIBLIOGRAPHY

1. UNGER, L.: Bronchial asthma, 1945, Chas. C. Thomas, Springfield, Ill.
2. FRENCH, M., and ALEXANDER, F.: Psychogenic factors in bronchial asthma, Psychosomatic Medicine Monographs, II, 1939 and IV, 1941.
3. BARACH, A. L.: The treatment of bronchial asthma and other chronic pulmonary diseases accompanied by constriction in the bronchial passageway, Med. Clin. N. Am., 1944, 339.
4. BEST, C. H., and TAYLOR, N. B.: The physiological basis of medical practice, Second Edition, 1940, The Williams and Wilkins Company, Baltimore, Md., p. 496.
5. WILSON, J. L., and FINDLEY, T.: Obstructive pulmonary emphysema, Med. Clin. N. Am., March 1944, 356.
6. PRINZMETAL, M.: The relation of inspiratory distention of the lungs to emphysema, Jr. Allergy, 1934, v, 493.

TREATMENT OF CARDIOVASCULAR SYPHILIS *

By H. Eisenberg, M.D.,† *Chicago, Illinois*

Introduction

Cardiovascular syphilis is frequently a problem to the internist. Ten to 15 per cent of cases of recognized cardiovascular disease, Blumgart [1] has estimated, are due to syphilis. Statistical studies by Moore [2] and by Leiby and Callaway and their coworkers [3] indicate that there are approximately 240,000 patients with syphilitic cardiovascular disease in this country at any one time and between 20 and 30 thousand die annually from it. Since the time of Ehrlich, the treatment of this disease has been a controversial matter, and remains so today notwithstanding the widespread and effective use of penicillin in therapy of early syphilis. Before discussing treatment, a brief review of the morbid anatomy and clinical signs of the disease is indicated.

Syphilis may appropriately be considered a general systemic infection with *Treponema pallidum,* in the course of which local lesions may occur, early or late, which may be striking enough to attract clinical attention. The most characteristic and widespread histologic changes, consequent to invasion by the spirochetes, consist of mononuclear cell infiltration in the perivascular lymph spaces. According to Longcope,[4] such changes may occur in the aorta during the secondary stage, concomitantly with the cutaneous manifestations. In cases of late syphilis at necropsy, Warthin [5] reported that 70 to 90 per cent showed histologic evidence of cardiovascular involvement. The high incidence of cardiovascular lesions in late syphilis, often clinically unrecognized, has been confirmed by postmortem studies made by Langer [6] and by Stokes [7]—Langer on over 23,000 autopsies. Antemortem clinical evidence of syphilitic cardiovascular disease existed in 39.5 per cent of Langer's cases, in 43 per cent of those reported by Lucké and Rea [8]; and in 16.2 per cent of a group of necropsy reports reviewed by Moore and his group.[9]

Clinical studies similarly reflect the incidence of clinically recognizable cardiovascular disease in late syphilis. Bruusgaard [10] estimated that 10 per cent of untreated cases of late syphilis, studied serologically and clinically, had clinically recognizable evidence of cardiovascular disease. In a group of 6,253 patients with late syphilis, either under observation or treatment for six months or longer by the Cooperative Clinical Group,[11] a clinical diagnosis of cardiovascular disease was made in 9.9 per cent. Turner's [12] study

* Read at the postgraduate course on cardiovascular disease, Northwestern University Medical School, Chicago, Illinois, as arranged by the American College of Physicians, April 23, 1947.

† Surgeon (R), U. S. Public Health Service.
Under the direction of Herman N. Bundesen, Senior Surgeon (R) (Inactive), U. S. Public Health Service; President, Chicago Board of Health.

of over 6,400 untreated cases of late syphilis showed an incidence of about 10 per cent; diagnosis of uncomplicated aortitis was made in 5.3 per cent, aneurysm in 1.2 per cent, and aortic insufficiency in 2.7 per cent.

Clinically significant pathologic changes appear to be restricted to the aorta and coronary ostia. In the aorta, early perivascular inflammatory reaction results in destruction of the elastic fibers of the media and consequent loss of resiliency. When this occurs in the aortic ring, dilatation of the ring with separation of the valve cusps occurs, followed by valvular incompetence. The same process of elastic tissue destruction and dilatation may involve the aorta diffusely. Diffuse aortitis is the most common and earliest form of syphilitic cardiovascular disease, located primarily supravalvular. When mesaortitis and dilatation are relatively localized, aneurysm results. A fourth type of cardiovascular involvement is consequent to intimal swelling about the coronary ostia. Carr [13] has estimated that less than 10 per cent of cases with aortic syphilis show clinical or electrocardiographic evidence of coronary involvement.

It might be well at this time to relate the anatomic changes just outlined to clinical signs commonly observed in cardiovascular syphilis. That these may occur early is attested by Brooks,[14] who has observed that cardiac arrhythmias, aortitis, and myocarditis frequently occur in secondary syphilis but will soon disappear if the case is given vigorous antisyphilitic therapy. Longcope [4] noted that clinically recognizable syphilitic aortitis may occur within a few months after primary infection, although the process is usually latent for longer intervals, up to 10 or more years.

Uncomplicated aortitis affecting the supravalvular region, with or without slight dilatation, is the most common and earliest cardiovascular change in syphilis.

This specific involvement will give rise to a characteristic physical sign —accentuation of the aortic second sound, described as tympanitic, drumlike, or of tambour quality—due to altered physical characteristics. This early clinical sign is usually accompanied by another just as characteristic, reflecting altered hemo-dynamics—a systolic murmur over the aortic area.

Cole, Usilton and their associates,[11] who reviewed material of the Cooperative Clinical Group, as well as Stokes,[15] consider a retrosternal pain of burning quality and typically unrelated to exertion as a characteristic symptom of uncomplicated aortitis. On the basis of experience at the Chicago Municipal Social Hygiene Clinics and at the cardiovascular disease clinic at Beekman Hospital in New York, we concur with the views of Dressler,[16] Maynard,[17] and Wilson [18] that the presence of this symptom is indicative of progression and of complication of the aortitis. The same can be said for coronary paroxysmal pain with characteristic radiation of angina-like attacks as well as of paroxysmal dyspnea, particularly nocturnal attacks. These physical signs relate to involvement of the coronary ostia, not to the coronary arteries themselves. In many of these cases one will find changes in the

electrocardiogram. They resemble those seen in coronary heart diseases, like chronic coronary insufficiency of the progressive type. Frequently, left ventricular failure follows, indicating a progressive cardio-aortic process.

The earliest detection of the aortic dilatation depends upon roentgen-ray examination, which is of particular value in patients less than 40 years of age without hypertension or other cardiac pathology. Fluoroscopic and roentgenographic examination should be made in all cases of late syphilis before diagnosis is completed. More advanced dilatation may manifest itself in classic supra-cardiac dullness or by causing suprasternal pulsation so that existing aneurysm may be suspected.

Aneurysm may be diffuse or saccular; the latter, when it occurs, is always of syphilitic origin. Diagnosis of this lesion depends upon both clinical and roentgenologic evidence.

The high degree of coexistence of cardiovascular and neurologic lesions in late syphilis is worth noting. It was found that neurosyphilis was present in 54 per cent of cardiovascular syphilitic cases studied at the Mayo Clinic,[19] and in 49 per cent of 6,253 cases collected by the Coöperative Clinical Group. Cases of neurosyphilis should, therefore, be carefully screened for cardiovascular lesions before treatment is undertaken.

A further progression of the syphilitic process may cause valvular incompetency with characteristic signs of a diastolic murmur over the aortic region of the heart with cardiac enlargement and high systolic with low diastolic blood pressure reading, followed by signs of congestive heart failure.

Early case-finding, adequate treatment, and systematic post-treatment observation of early syphilis is the most effective means of preventing cardiovascular syphilis. The increasingly wide application of more effective treatment since Ehrlich's introduction of arsenotherapy in 1910 appears, in the opinion of Thompson [20] and others, to be reflected in a decreasing prevalence of syphilitic cardiovascular disease during the last two to three decades—an opinion expressed also by pathologists.[21]

It seems reasonable that since penicillin has been used in syphilis, a large number of patients have probably been treated inadequately; many of those may have disappeared from observation and possibly will not come under medical observation again before they show late signs of syphilis, and particularly, cardiovascular syphilis. An even greater menace exists in the fact that oral penicillin preparations have become available and may be used for self-medication. Because this drug in relatively small doses may cause remission of cutaneous lesions without in any sense arresting the disease, there is good reason to expect that disastrous results may come to the attention of internists and cardiologists within a few years.

Without further dwelling upon the importance of the underlying syphilitic pathology and symptomatology and the relationship of these two in order to arrive at a correct diagnosis and raise the index of suspicion, let us now consider the application of chemotherapy to the treatment of syphilitic cardio-

vascular disease. Reported experience with penicillin is limited. It appears, however, that considerations applying to conventional therapy with arsenic and bismuth preparations are valid for penicillin as well.

Therapy with Metallic Compounds

Soon after the introduction of salvarsan, fatalities during the course of treatment in early and late syphilis were observed. These were attributed to myocardial damage or to ventricular fibrillation, due to the higher toxicity of the older drugs. This was substantiated by the investigations made by Reid,[22] who found that the arsenicals decrease the rate of conduction in the heart and shorten the refractory period in the heart muscle.

It was also observed that the phenomenon of therapeutic shock, or the Herxheimer reaction, might be implicated in the etiology of occlusion of the coronary ostia, aneurysmal rupture, or abrupt cardiac decompensation. The Herxheimer reaction may be characterized as a transient exacerbation of the local lesions of syphilis as an early response to treatment. It has been discovered empirically that this phenomenon may be minimized by the induction of therapy with small, but constantly increasing, doses. Another potential hazard of treatment in cardiovascular syphilis is the so-called therapeutic paradox, to which attention has been directed by Wile.[23] In this state, the too-rapid healing of syphilitic lesions with consequent scar-tissue formation may result in anatomic healing but functional deterioration. Sudden encroachment on the coronary orifices during therapy presents particular risk in this connection.

Because of early unfavorable results, arsenotherapy fell into relative disrepute until the introduction of less toxic compounds, notably neoarsphenamine and the even less toxic oxophenarsine hydrochloride, which appeared on the market under the proprietary name of Mapharsen.

The scheme of treatment should depend upon the anatomical diagnosis and functional state of the patient. In the presence of uncomplicated aortitis, conventional therapy with alternating courses of arsenical and bismuth compound may be recommended. The first course may be one of the arsenicals, administered at weekly intervals and beginning with small but increasing amounts. At the Municipal Social Hygiene Clinic, oxophenarsine is being employed in an initial dose of 0.03 gram, increasing at weekly intervals to 0.06 gram, with weekly injections of insoluble bismuth 0.2 gram given at the same time. Bismuth may also be given alternately between courses of eight weekly arsenicals for 10 weeks, the treatment to last from 9 to 12 months, giving about 24 arsenicals and 40 bismuth injections. Untoward effects and severe Herxheimer reactions are uncommon in uncomplicated aortitis. Schottmuller [24] and others have also given the arsenicals without preliminary preparation with bismuth or other anti-syphilitic drugs without harmful effects. To begin with the arsenicals in this form of aortic syphilis is contrary to the Moore [25] and the Johns Hopkins School of Medicine, which

advocated preparatory heavy metal for a period of 12 weeks, to be followed by the arsenicals in gradual increasing doses. It is important to note that the stage of uncomplicated aortitis is the most favorable time for treatment. Progression may be arrested by adequate therapy; and dangerous complications of treatment are minimal.

In the presence of aneurysm, valvular lesions, or electrocardiographic evidence of coronary damage, the induction of therapy must be much more gradual. Bismuth should be administered at weekly intervals for at least three months prior to the use of arsenicals. At the discretion of the therapist, bismuth may be preceded by or supplemented with appropriate, graduated doses of potassium iodide. In the absence of reactions and the presence of adequate cardiac reserve at the end of such a period of preliminary therapy, an arsenical compound may be begun in graduated doses in the manner described before. It might be well to state here that patients with complaints of substernal pain, treated in this manner, will usually feel remarkably improved physically and their symptoms may disappear completely.

If there is a history of cardiac decompensation, or if congestive failure has occurred prior to or during the course of specific syphilotherapy, specific chemotherapy should be abandoned entirely or not begun until adequate cardiac reserve has been reëstablished by customary methods of treatment such as digitalis, diuretics, and bed rest. Impaired renal function consequent to decreased circulatory efficiency is a distinct contraindication to the use of compounds as toxic as those containing arsenic or bismuth. And in the presence of circulatory failure, exposure of a critically impaired cardiovascular system to the added hazard of Herxheimer reaction or therapeutic paradox cannot be justified, whether as a consequence of arsenicals or of penicillin therapy.

Experience of the coöperative clinics, as reported by the Committee on Medical Research and the U. S. Public Health Service [26] concerning treatment of early syphilis with penicillin, indicates that the incidence of febrile Herxheimer reactions is high with this drug. Moore,[27] summarizing experience at the Johns Hopkins Hospital and elsewhere, recommends the following schedule of penicillin therapy for cardiovascular syphilis: aqueous solutions of penicillin are administered intramuscularly at three-hour intervals. During the first day, the individual dose is limited to 1,000 units; during the second, increased to 5,000 units; next day to 10,000 units; 25,000 on the fourth and a standard individual dose level of 50,000 units on the fifth day, which is maintained until the twenty-second day to a total of 8.9 million units. No instances of therapeutic shock were observed in a group of 12 cases of aortic regurgitation, aneurysm, or syphilitic aortitis with coronary osteal stenosis and angina of effort, which he treated by this program. One patient with coexistent paresis died on the fourth day, presumably from heart failure. The aorta showed plaques of syphilitic aortitis, each containing a

large fresh hemorrhage. No other patient was worse after therapy. In Moore's cases, the serologic response was, like that of late syphilis, in general, inappreciable.

Russek,[28] at U. S. Marine Hospital in Staten Island, used doses of 40,000 units every two hours for 85 doses, in 15 cases of aortitis and aneurysm, without any undue reactions.

Dolkart and Schwemlein [29] undertook treatment of two patients with aortic insufficiency, one of whom had associated rheumatic heart disease, frequent anginal attacks, and several previous episodes of congestive failure. Treatment was discontinued because of the development of fresh anginal attacks, and ventricular extrasystoles, in the first case. The second patient developed intermittent precordial distress after four days and was given no more therapy.

The experience of Peters [30] at the Intensive Treatment Center of the Chicago Health Department, and our own experience at the Municipal Social Hygiene Clinic, have been quite favorable. At the Chicago Intensive Treatment Center, 20 cases of neurosyphilis with coexisting cardiovascular involvement have been treated with several programs of aqueous penicillin. Some cases were started with 5,000 units; the dose was gradually increased to 10,000, 20,000, 30,000 and 40,000 units every three hours up to a total of 6,000,000 units. Other cases were given 40,000 units every three hours, for a total of 2,400,000 units, with few complications.

At the Municipal Social Hygiene Clinic, about 20 patients with uncomplicated aortitis have been treated with penicillin in the oil and beeswax vehicle devised by Romansky. An initial dose of 100,000 units in one injection is given, and increased by 100,000 units after the third and fifth day to 300,000 units to a total of 4,500,000 units in 15 to 20 days. We have observed no untoward reaction. No data on extended observation after treatment are available as yet; the longest period during which any of our patients has been observed is four months. Final time-dose relationship has not as yet been established. Wile,[32] writing in the Rapid Treatment Center bulletin, again has cautioned us against too intensive methods in the treatment of cardiovascular syphilis. After the disease has reached a clinical horizon, treatment reactions are more apt to occur. This relates to either the arsenicals or penicillin, both of which are fast-acting drugs.

Conclusion

In conclusion, early case-finding, adequate treatment, and careful observation of early syphilis are important in prevention of late cardiovascular disease. Selection of treatment in the late case depends upon accurate diagnosis of anatomic changes and evaluation of functional reserve. Uncomplicated aortitis and some cases of aneurysm may be treated with low risk and reasonable expectation of success with conventional alternating courses of arsenic and bismuth compounds. In the presence of valvular disease,

aneurysm or history of congestive failure, treatment must be initiated with bismuth for two to three months, followed by gradually increased doses of an arsenical compound. In all cases, initial doses must be graded to minimize the risk of severe Herxheimer reactions. In the presence of decompensation and until the establishment of adequate cardiac reserve by conventional means, no form of syphilotherapy should be employed. After establishment of cardiac compensation, gradually increased doses of bismuth should be given for at least three months, followed by weekly injections of 0.005 gm. of mapharsen, increasing to 0.03 gm. In cases of repeated congestive failure or myocardial and coronary involvement, as evidenced by electrocardiographic records, only mercury or bismuth is indicated—never any arsenicals. Evidence from records of the Chicago Board of Health, Johns Hopkins Hospital and Staten Island Marine Hospital indicates that penicillin begun with graded doses may be used in uncomplicated aortitis and aneurysm with acceptably low risk. More complete evaluation of penicillin in syphilitic cardiovascular syphilis cannot be made at present.

BIBLIOGRAPHY

1. Blumgart, H. L.: Detection and treatment of cardiovascular syphilis, New England Jr. Med., 1940, ccxxiii, 443.
2. Moore, J. E., Danglade, J. H., and Reisinger, J. C.: Diagnosis of syphilitic aortitis uncomplicated by aortic regurgitation of aneurysm, Arch. Int. Med., 1932, xlix, 753.
3. Leiby, G. M., Callaway, J. L., and Fleming, W. L.: Diagnosis and management of asymptomatic uncomplicated aortitis, North Carolina Med. Jr., 1940, i, 301.
4. Longcope, W. T.: Syphilitic aortitis, its diagnosis and treatment, Arch. Int. Med., 1913, xi, 15.
5. Warthin, A. S.: The lesions of latent syphilis, Southern Med. Jr., 1931, xxiv, 273.
6. Langer, E.: Die Haufigkeit der luetischen Organveranderungen, insbesondere der Aortitis luetica, Munchen. med. Wchnschr., 1926, lxxiii, 1782.
7. Stokes, J. H.: Modern clinical syphilology, 1944, W. B. Saunders Co., Philadelphia, p. 900.
8. Lucké, B., and Rea, E.: *in* Stokes, J. H.: Modern clinical syphilology, 1944, W. B. Saunders Co., Philadelphia, p. 896.
9. Moore, J. E.: See reference 2 above.
10. Bruusgaard, E.: Summary of Bruusgaard's data as to ultimate outcome of untreated syphilis. From Moore, J. E.: Modern treatment of syphilis, 1943, Charles C. Thomas, Springfield, Ill., p. 38.
11. Cole, H. N., and Usilton, L. J.: Cooperative clinical group; studies in the treatment of syphilis, Ven. Dis. Inform., 1936, xvii, 95.
12. Turner, T. B.: *In* Stokes, J. H.: Modern clinical syphilology, 1944, W. B. Saunders Co., Philadelphia, p. 896.
13. Carr, J. G.: The gross pathology of the heart in cardiovascular syphilis, Am. Heart Jr., 1930, vi, 30.
14. Brooks, H.: The treatment of cardiovascular syphilis, Warthin Anniversary Volume, Wehr, Ann Arbor, 1927, p. 117.
15. Stokes, J. H.: Modern clinical syphilology, 1944, W. B. Saunders Co., Philadelphia, p. 907.
16. Dressler, M.: Cardiovascular syphilis; an approach to early clinical recognition and early treatment, Conn. State Med. Jr., 1945, ix, 848.

17. MAYNARD, E. P., JR.: Diagnosis of cardiovascular syphilis, Brooklyn Hosp. Jr., 1940, ii, 69.
18. WILSON, R., JR.: Studies in syphilitic cardiovascular disease. I. Uncomplicated syphilitic aortitis; an asymptomatic condition, Am. Jr. Med. Sci., 1937, cxciv, 178.
19. MAYO CLINIC: *In* STOKES, J. H.: Modern clinical syphilology, 1944, W. B. Saunders Co., Philadelphia, p. 931.
20. THOMPSON, W. P., CORNEAU, W. J., and WHITE, P. D.: The role of the treatment of syphilis in the prevention of cardiovascular involvement, Am. Heart Jr., 1939, xvii, 286.
21. Private communication to author.
22. REID, W. D.: The mechanism of the toxic action of arsphenamine on the heart, Jr. Am. Med. Assoc., 1925, lxxxiv, 883.
23. WILE, U. J.: The treatment of the syphilitic liver and heart, a therapeutic paradox, Am. Jr. Med. Sci., 1922, clxiv, 415.
24. SCHOTTMULLER, H.: On the treatment of syphilis of the aorta, Am. Jr. Syph., 1925, ix, 1.
25. MOORE, J. E.: The modern treatment of syphilis, 1943, Charles C. Thomas, Springfield, Illinois, p. 294.
26. Committee on Medical Research and the U. S. Public Health Service: The treatment of early syphilis with penicillin, Jr. Am. Med. Assoc., 1946, cxxxi, 265.
27. MOORE, J. E.: Penicillin in syphilis, 1947, Charles C. Thomas, Springfield, Illinois, p. 195.
28. RUSSEK, H. I., CUTLER, J. C., FROMER, S. A., and ZOHMAN, B. L.: Treatment of cardiovascular syphilis with penicillin, Ann. Int. Med., 1946, xxv, 957–959.
29. DOLKART, R. L., and SCHWEMLEIN, G. X.: The treatment of cardiovascular syphilis with penicillin, Jr. Am. Med. Assoc., 1945, cxxix, 515–516.
30. Private communication from E. E. Peters to author.
31. To be published.
32. WILE, U. J.: Cardiovascular syphilis, Rapid Treatment Center Bulletins, 1945, ii, 12.

MANAGEMENT OF DIABETES MELLITUS: AN ANALYSIS OF PRESENT-DAY METHODS OF TREATMENT *

By HERMAN O. MOSENTHAL, M.D., F.A.C.P., *New York, N. Y.*

A COMPLETE life span, full activities and freedom from any physical or mental impairments are possible for the diabetic today. All diabetics do not reach this goal, but many of them do. The problem before us is: how should we manage diabetics to keep them in normal health?

Mass control, statistical evaluations and their mechanical interpretations have set the pace for a regimented therapy of a number of diseases. Diabetes and hypertension have been particular victims of this method of approach. Both patients and doctors are under pressure to enforce one or the other rigid system of treatment for all diabetics without regard to their personality or the type of diabetes involved. Such one-track methods of diabetes control have been advocated by individual physicians and some medical groups. Life insurance acceptability, from the company's point of view, may be judged adequately from a collection of 5,000 cases. However, there is no safety or satisfaction for those diabetics who suffer harm because their particular case does not fit the plan prescribed by their medical adviser.

There are three sects endorsing special systems of diabetes management. I am naming them according to informal, frequently used terms:

1. Purists
2. Middle of the Roaders
3. Free Dieters

The diabetic state of any patient may change from month to month, or year to year, and a form of treatment which is beneficial at one time, may be distinctly harmful at another. No single system of diabetes control meets all situations at all times; diabetes is not a disease of unitarian etiology, nor of predictable development.

The basic principles of the three sects advocating fixed procedures for diabetes therapy are shown in table 1. Diet, blood sugar and glycosuria are the three pivotal expedients by which diabetes control is accomplished. These will be taken up separately and the ideas concerning them can be applied to the requirements of each patient. This method of analysis encourages greater freedom of action by the physician and more rational application of therapy than if all three clinical yardsticks were rigidly fixed and delivered in a sealed container like army rations.

* Read at the New England Postgraduate Assembly, October 30, 1947.

TABLE I

Basic Principles of the Three Sects Advocating Fixed Procedures for Diabetes Therapy

	Diet	Blood Sugar	Glycosuria	Special Notes
Purists	No sugar, meticulously calculated and measured, adequate for maintenance	Normal level constantly maintained	Completely checked	Some regard this as a temporary measure to aid recuperation of the islet cells; others insist on it as a permanent plan
Middle of the Roaders	No sugar, about 150 gm. carbohydrate, adequate protein	Normal level as far as possible, at least at intervals during the day	Most specimens sugar free, some may at times contain sugar, no more than 10–20 gm. in 24 hours.	Avoid hypoglycemic reactions
	High carbohydrate, no sugar, low fat			
Free Dieters	Carbohydrates, including sugar, as desired	Blood sugar level disregarded	Glycosuria disregarded	Protamine zinc insulin once a day; no other form of insulin

DIET—FOODS AND THEIR USE IN DIABETES

Caloric Requirements. Suitability of the caloric intake must be judged by the weight of the patient. Fewer calories than those deemed requisite on scientific grounds are nearly always sufficient. The details are given in table 2. Leanness in all human beings is conducive to longevity and in addition it offers the diabetic the possibility of amelioration of his disease.[1]

TABLE II

Caloric Requirements

Recommended daily caloric intake by the Committee on Foods and Nutrition, National Research Council

	Man (70 Kg.)(154 lbs.)	Woman (56 Kg.)(123 lbs.)
Sedentary	2500	2100
Moderately active	3000	2500
Very active	4500	3000

In practice caloric requirement should be judged according to weight control (quantitative nutrition). Average caloric needs have been found to be:
Men—city dwellers—executives, doctors, bus drivers, etc.
1800 to 2100 calories
Women—housewives, clerical workers, etc.
1500 to 1800 calories
Growing children, Hard manual workers } much higher calories are essential.

Carbohydrates. Sugar (or sugar-containing foods) should be avoided since their ingestion results in an explosive rise of blood sugar that puts a fluctuating strain upon carbohydrate metabolism to which the diabetic does not respond, either with or without insulin. For psychological adjustments, especially in children, desserts or soft drinks may, on occasion, be substituted

for the equivalent of starchy food in the diet, or compensated for by supplementary doses of insulin. Sugar may be eaten by some diabetics without producing glycosuria or hyperglycemia while they are receiving no insulin or only small doses. There is no reason why they should not receive sugar. However, such cases are very rare and it is a matter of trial and error to ferret out these patients.

A diet satisfactory for an indefinite period may be provided by a daily intake of 150 grams of starch. This amount allows for one slice of bread for each of four meals, one helping of the starchy, 20 per cent vegetables, e.g. potato, rice, macaroni; one glass of milk; a helping of the 10 per cent vegetables, onions, carrots, beets, etc., and two helpings of the 10 per cent fruits, e.g. oranges, grapefruit, besides the 3 per cent vegetables and the foods containing protein and fat only. Such a diet may be regarded as a normal carbohydrate diet.

High carbohydrate diets containing 250 to 300 grams of carbohydrate, as advocated by some clinicians, for universal use in diabetes, undoubtedly are applicable to growing children and those engaging in hard manual labor. However, in most adults such diets tend to result in obesity and their control by insulin is more difficult than with a lower starch intake.

The variable amount and kind of carbohydrate consumed on the free diet regime make it impossible to control glycosuria and it is only if unlimited urinary sugar is to be sanctioned that such a procedure can be endorsed.

TABLE III

Carbohydrates in the Diabetes Diet

Sugar and sugar containing foods to be avoided, except for psychological adjustments, particularly in children.

Carbohydrate 150 gm. provides an ample and palatable diet for continued use.

Carbohydrate 200 to 300 gm. is usually more than most persons desire to eat. It is advocated for routine use in the so-called high carbohydrate diets. Glycosuria on such diets is as a rule difficult to control. High carbohydrate diets are applicable to growing children, athletes and hard manual laborers, but not to sedentary persons or those taking moderate exercise.

Free diets sanctioning variable amounts of all kinds of carbohydrate make it difficult, practically impossible, to keep glycosuria within reasonable bounds.

Proteins. The integrity of the body depends upon an adequate assimilation of proteins. The belief that proteins, especially meats, and particularly red meats, tend to elevate blood pressure and are a cause for arteriosclerosis, has been proved erroneous. A diet deficient in protein results in degenerative changes in the kidneys and presumably other tissues,[2] in anemia and in hypoproteinemia. Degenerative lesions of arteries precede the deposit of cholesterol in the production of arteriosclerosis and it is possible that insufficient protein may be partly responsible for the more frequent presence of arteriosclerosis in diabetics than in normal persons. Protein deficiency may have a dual origin in the diabetic, through a scant intake and because of insufficient insulin. Consequently not only the amount of protein eaten, but also the necessary insulin coverage demand attention for the conservation of body tissues. It has been shown that protamine zinc insulin brings about

far better results in pulmonary tuberculosis complicating diabetes than does unmodified insulin.[3] The reason for this is that each dose of unmodified insulin checks protein destruction and loss for four hours only, whereas every injection of protamine zinc insulin accomplishes this for 24 hours.[4]

Recently the deficiency of serum proteins has been stressed as an accompaniment of and as a cause of the much dreaded diabetic retinopathy.[5] For the maintenance of health and strength and for the prevention of many of the complications of diabetes the preservation of the body proteins is of great importance. The protein intake should exceed rather than be less than the traditional gram per kilo and should include animal proteins in liberal amounts. The diet slogan: meat, fish or eggs at each meal, has decided merits. It is well known that marked glycosuria is accompanied by protein destruction. This can and should be checked by insulin administration effective throughout the 24 hours.

TABLE IV

Proteins in the Diabetes Diet—Qualitative Nutrition

When nutrition or maintenance is considered body weight is always the lay criterion and often the medical standard. However, there are two kinds of nutrition, quantitative, which is of little value, and qualitative, which is essential.

Quantita'ive nutrition is the accumulation of fat.

Qualitative nutrition depends on effectual protein integration.

It is judged by hemoglobin, red blood cell count and level of serum proteins.

It is maintained by an ample protein intake, including meats, 75 to 120 gm. per day. In diabetes prevention of inordinate glycosuria and adequate insulin dosage check protein destruction.

Good qualitative nutrition favors the healing of infections, e.g. tuberculosis, and will do much to prevent the dreaded present day complications of diabetes: arteriosclerosis, nephritis and retinopathy.

Fats. The use of fats in the diabetes diet has been decried with excessive vehemence. The minimum carbohydrate and protein, but extremely high fat diets as originally advocated by von Noorden and later by Newburgh, are at present endorsed by no one. A high fat intake is accredited with diminishing carbohydrate tolerance and with the production of arteriosclerosis. Both of these drawbacks deserve consideration. On the other hand, a certain amount of fat is a necessary nutrient. The provision of fat soluble vitamins and of calcium can be accomplished only by certain fatty foods. In antiobesity diets it has been found advisable to prescribe a minimum of one egg and a glass and a half of milk a day. The diabetic, except when calories are restricted because of obesity, may have more of these and the addition of some butter and cheese is desirable. The adjustment of the fat intake in the usual restricted carbohydrate diets of diabetes is the obvious means of weight regulation, unless the amount of alcohol consumed is a factor.

Alcohol. Alcohol is a valuable form of food in diabetes. It is a good source of calories; it does not form sugar; it has so-called anti-ketogenic properties. The alcoholic beverages containing sugar, especially beer, champagne and cocktails, should be avoided, while whiskey, brandy, dry wines

and others free of sugar may be taken as desired. The control of loss or gain of weight by the regulation of alcohol is self-evident.

TABLE V

Fats and Alcohol in the Diabetes Diet

Fats

High fat intake reduces glucose tolerance and produces arteriosclerosis.
Some fat is required for the provision of fat soluble vitamins and calcium.
Minimal of fatty foods is: 1 egg and 1½ glasses of milk a day.
More of these as well as butter and cheese are advisable.
In the diabetic, adjustment of the fat intake serves to regulate weight.

Alcohol

Sugar-containing alcoholic beverages—beer, champagne, cocktails, are forbidden.
Whiskey, brandy, dry wines may be taken.
Alcohol is a good source of calories, does not form sugar and has anti-ketogenic properties.
Weight control by prescribing or withholding alcohol should be considered.

BLOOD SUGAR

Some plans of diabetes management call for a blood sugar always at normal levels, others allow intermittent hyperglycemia, while the free diet school pays little or no attention to the sugar in the blood. From the many clinical and experimental observations it appears that each of these proposals is applicable in certain types of diabetes.

A low blood sugar persistently maintained will promote the healing of hydropic lesions in the pancreatic islets.[6] It is thus shown that hydropic degeneration is reversible. Little is known about the occurrence of such changes in the human pancreas. However, the rehabilitation of the pancreatic function in diabetes of recent origin whether in children,[7] the obese [8] or after a particular insult, e.g. an acute infection, points to a restoration of the beta cells in the islands of Langerhans. Such types of diabetes should be accorded the most painstaking care and a normal blood sugar should be maintained in them for a period of weeks after the insulin requirement has ceased to diminish or the tolerance to ingested carbohydrates no longer increases. When the insulin need is less than 30 units, a purist objective should be continued for reasons given in the next paragraph.

When all the beta cells in the pancreatic islets have been destroyed without hope of bringing them back to activity then a perfect control of the blood sugar does not benefit pancreatic function. This has been shown for alloxan diabetes (fibrotic degeneration of the islet cells) in experimental animals and by clinical studies. How to judge this state of affairs in patients is a difficult problem. The only available guide at the present moment is the knowledge that after total pancreatectomy in man the insulin requirement is not more than 30 to 40 units a day.[9] When this amount or more of insulin becomes necessary for the effective control of chronic diabetes then the clinician is justified in assuming that the pancreas has ceased producing insulin. Under such circumstances the middle of the road pattern of intermittent hyperglycemia appears warranted.

The insulin need of many diabetics above 40 units per day is attributed to a vague, unsatisfactorily explained condition termed insulin resistance. The specific means for the amelioration, let alone cure, for this disturbance, is not at hand. As a rule these cases do better with a restricted carbohydrate intake. When they take a high carbohydrate or a free diet their insulin requirement is prone to go up enormously. An elevated blood sugar without glycosuria may prevent restoration to normal of hydropic lesions in the beta islet cells. However, hyperglycemia in itself does not impair immunity, has little or nothing to do with the diabetic's state of resistance or susceptibility to infection, does not inhibit the growth of tissue culture, does not interfere with the healing of wounds or the recovery from infections, and promotes the metabolism of glucose.[10] Moreover, there is some evidence that a concentration of blood sugar greater than normal is necessary for the utilization of carbohydrates in diabetics.[11] Consequently, it would appear that hyperglycemia not associated with glycosuria, is objectionable only insofar as it has an unfavorable effect on the pancreas. This, in practice, would apply only to recent diabetics who have hydropic lesions, which are reversible, and to those chronic diabetics who have retained some insulin-producing islet cells—that is have an insulin requirement of less than 30 units. There is an apparent fallacy in this reasoning and that is the possibility of some remaining pancreatic tissue when the insulin requirement is 40 units or more because of concomitant insulin resistance. However it offers the best available starting point for the application of more relaxed types of treatment and relief from excessive nervous tension incident to the purist regime.

Hypoglycemia. Hypoglycemic, often called insulin, reactions result from a deficient supply of glucose to the brain. The viability of the tissues of the central nervous system depend upon the presence of glucose in the blood. When the blood sugar becomes very low—hypoglycemia—impairment of cerebral functions follows. Headaches, dizziness, sweating are among the first symptoms; progression to unconsciousness, convulsions and death may ensue. Besides the direct effect of hypoglycemia on the brain, the mal-effect and strain imposed by the outpouring of epinephrine engendered by blood sugar depression must be considered.

The lesions in the fatal cases are severe: petechiae and extensive cerebral hemorrhages, large areas of encephalomalacia and cyst formation.[12] It is self-evident that in diabetics who are subject to transitory hypoglycemic episodes, the morphological pathology cannot be determined. However, in experimental animals this can be done and months after recovery from hypoglycemic reactions, areas of demyelination, encephalomalacia and glial reactions are found.

All this leads to the conclusion that any hypoglycemic reaction, however mild, may entail petechial or larger hemorrhages that are prone to heal and leave no clinical effect, though some damage necessarily remains and may be cumulative with recurrent attacks. Not only the brain may be thus involved

but other tissues as well. I am thinking particularly about the eye grounds and the so-called diabetic retinopathy. Some cases of pheochromocytoma with paroxysmal hypertension have developed retinal hemorrhages. It is well established that hypoglycemic reactions are associated with a mobilization of epinephrine, thus being a potential cause of bleeding in the eye grounds.

This reasoning has been applied with apparent success to the treatment of diabetic retinopathy. Two cases may be mentioned. In each of them the hemorrhages were progressively aggravated and in each of them the bleeding ceased and the existing hemorrhages disappeared—in one patient with complete restoration of vision, and in the other with considerable improvement. The first was a young woman in her thirties. She had a "brittle" diabetes and could not be rendered sugar free without encountering hypoglycemic reactions; the insulin was so regulated from day to day that reactions were avoided, glycosuria was allowed but never to such a degree that polyuria occurred. The second was a man of 70; for one year he had recurring retinal hemorrhages; he had an attendant nurse and it was an easy matter to maintain a sugar-free urine and a normal blood sugar; he became subject to considerable dizziness which disappeared when a higher than normal blood sugar and a moderate glycosuria were established; simultaneously the retinal hemorrhages ceased and vision improved.

The avoidance of hypoglycemia furnishes a second means by which diabetic retinopathy and possibly other complications of diabetes may be prevented and rectified. The first was the maintenance of qualitative nutrition.

Every bit of evidence at hand points to the damaging effect hypoglycemic reactions probably have. Though there may be no signs of injury after many minor or even major low blood sugar incidents, it has to be conceded that their summation may lead to harm just as a prize-fighter who is struck on the head often enough becomes "punch drunk." Furthermore, the fortuitous location of a hemorrhage has a distinct bearing. Bleeding may have little significance in a silent region of the brain, but in the motor areas may cause paralysis; in the periphery of the retinae, petechial bleeding goes unnoticed, whereas when the macular region is involved, loss of vision results.

For the above reasons when insulin is used the major consideration for the carrying out of successful long range treatment is the avoidance of hypoglycemic reactions. What has been stated concerning the vulnerability of the brain and the retinae to insulin over-effect, may also apply to the heart and the kidneys which are the other organs prone to be damaged in diabetes.

Recently it has been shown that all diabetics of 25 years' duration exhibit one or more complications: retinopathy, albuminuria, hypertension, myocardial degeneration.[13] Dolger has rendered a valuable service in collecting two hundred cases which yielded these results. Unfortunately from these observations the impression has been broadcast that all diabetics are afflicted

TABLE VI

Blood Sugar—Regulation in Diabetes

A maintained normal blood sugar level will bring about a complete or partial reversal of the pancreatic lesions in diabetes of recent onset.

When diabetes becomes chronic and the insulin requirement exceeds 30 units, intermittent hyperglycemia and moderate glycosuria will usually not cause progressive damage to the pancreas.

Hypoglycemic (insulin) reactions are a cause for petechial and larger hemorrhages in the brain and retinae. The summation of repeated injuries of this sort may result in encephalopathy and retinopathy. The avoidance of hypoglycemic reactions therefore becomes of paramount importance. Such a step and the maintenance of qualitative nutrition are at present the only means suggested for preventing and remedying the complications of diabetes.

not only with complications but with complete physical disability. At the moment I can recall only three cases that have had diabetes for a quarter of a century. While all three have had complications which might be ascribed to diabetes, they are all active and in good health. One is a woman, aged 70, caring for her household and taking an extraordinary and effective interest in her children; one is a man, aged 68, employed in one of the large banks; and the third is a young woman who is the mother of four thriving children. There is no invalidism in any of these three diabetics. It is unduly pessimistic to regard all diabetics as doomed to inevitable decrepitude; a prospect for normal life and health is warranted for most of them.

GLYCOSURIA

In diabetes glycosuria results from hyperglycemia. Consequently, as discussed under blood sugar, there are the diabetics of recent onset and the mild cases in whom a normal blood sugar and freedom from glycosuria may serve to heal hydropic lesions in the islet cells and prevent degeneration of pancreatic tissues from overstrain. Most clinicians agree on the desirability of a purist procedure in such patients. By some the same system of management is applied to all diabetics.

A moderate glycosuria, like hyperglycemia, is harmless when no functioning pancreatic tissue remains. The middle of the roaders recommend that there be no more than 10 to 20 grams of sugar in the urine per day and that the glycosuria be intermittent.[14] This is a sane, realistic recognition of the fact that diabetics are human beings and that the time and worry entailed in keeping the control of blood sugar and urine every hour of the day, every day of the year, is often not compatible with normal living. In some cases, especially elderly individuals, a constant glycosuria becomes a necessity because of hypoglycemic reactions at inordinately high blood sugar levels; in such instances the glycosuria should be maintained at a level of less than one per cent. Whenever glycosuria is sanctioned, special care must be exercised to check polyuria.

The free diet advocates condone limitless glycosuria while the diabetic receives protamine zinc insulin.[15] Tolstoi, the originator of this plan, believes that glycosuria may be neglected provided there is maintenance of

weight, freedom from all symptoms of diabetes: thirst, polyuria, frequency of urination, hunger, weakness, fatigue, polyphagia, pruritus of the genitals and visual disturbances; absence of ketone bodies in the urine. If these criteria are observed this actually ceases to be a new pattern for the treatment of diabetes, but means close adherence to the principles of the "middle of the roaders."

The fascinating simplicity and convenience of a free diet and limitless glycosuria have actuated doctors, patients and Tolstoi himself into carrying out a form of treatment that is contrary to valid principles of diabetes management. In practice the free dieters do not follow the rules set down in the original exposition of the "newer concepts in the treatment of diabetes mellitus." It is impossible to take up all the points in detail. Discussion will be confined to only one, that is polyuria. Polyuria existed in some of the cases published by Tolstoi.

Polyuria, loss of fluid and resulting desiccation have a far-reaching effect on the body economy. Outside of the well-known extreme dehydration and its devastating effect in diabetic coma there are comparatively few observations that bring home the results of desiccation. There are three striking ones which may be cited. It is well known that life without fluid is a matter of hours, while life without food lasts for days. In 1860 Weir Mitchell, one of the founders of functional neurology and the author of some excellent novels, showed that in frogs, hyperglycemia in itself had no effect upon the ocular lens, but when the excess of sugar was supplemented by desiccation, rapid formation of cataract took place which promptly disappeared when the frogs were immersed in water.[16] Ludwig Aschoff, one of the greatest pathologists, claimed that desiccation induces arteriosclerosis.[17]

An example of a patient arbitrarily taking on a free diet scheme is that of a girl, aged 14, who was under satisfactory control for her diabetes. While on a summer vacation for 10 weeks she relinquished all dietary precautions though maintaining her insulin injections. The daily insulin dosage was protamine zinc insulin 40 units and globin insulin with zinc 20 units by separate injections. The free dieting resulted in nocturia three times, indicating polyuria, a vaginal discharge, 2.5 per cent glucose in the urine, blood sugar 422 mg. per 100 c.c., and evident physical and mental deterioration. All these inroads were promptly rectified when a constant diet suitable to her needs and acceptable to her tastes was provided.

The interpretation of the free diet plan generally entertained by doctors is to allow all foods while insulin is administered. A tabulation, over a considerable period, of the effects of free diets as carried out under medical guidance, other than mine, yielded these data: Out of 56 females, nine developed pruritus vulvae, and out of 94 children, 11 became bed wetters when they had not been so before.

The teachings of Tolstoi have engendered the idea that the kind and amount of daily food may be adjusted to the patient's desire of the amount

and that limitless glycosuria is of no consequence while the diabetic receives protamine zinc insulin. Such a plan of treatment results in polyuria, pruritus vulvae and other symptoms of diabetes. If according to Tolstoi's original postulates, "freedom from all symptoms of diabetes," is to be achieved, the diet must be more or less constant and the glycosuria must be within reasonable bounds. In other words the free diet idea when applied in accordance with Tolstoi's "guiding principles" is, in reality, a middle of the road procedure and a warranted form of therapy for some but not all, diabetics. The free diet plan carried out according to lax and liberal interpretations is a menace to the diabetic patient.

TABLE VII

Glycosuria—Regulation of Urinary Sugar in Diabetes

This largely parallels the statements made concerning hyperglycemia.
A maintained normal blood sugar level and freedom from glycosuria will bring about a complete or partial reversal of the pancreatic lesions in diabetes of recent onset.
When diabetes becomes chronic and the insulin requirement exceeds 30 units, then intermittent hyperglycemia and moderate glycosuria will not cause progressive damage to the pancreas.
In diabetics subject to hypoglycemic reactions at high blood sugar levels it is advisable to maintain a moderate glycosuria of less than 1 per cent.
The free diet plan, as usually interpreted and carried out, permitting limitless glycosuria, is a menace to the diabetic patient.

SUMMARY AND CONCLUSIONS

A three-point plan for the management of diabetes is proposed. This embodies the advantages of all the current creeds for diabetes treatment and has a factual regard for the needs of the individual patient.

1. In diabetes of recent onset a normal blood sugar level and freedom from glycosuria are imperative for the rehabilitation of the injured cells in the pancreatic islets, also in those diabetics whose insulin requirement is less than 30 units, so that the remainder of the pancreatic tissue shall not be damaged by overstrain. A normal blood sugar concentration and avoidance of glycosuria are desirable in all cases but the paramount consideration is freedom from hypoglycemic reactions which may necessitate the countenancing of hyperglycemia and glycosuria, but never polyuria.

2. Conservation of qualitative nutrition as measured by the hemoglobin percentage, the red blood cell count and the level of the serum proteins; avoidance of quantitative over-nutrition, that is, obesity.

3. Adjustment of food intake, diet calculations, auto-urine analysis and medical supervision so that the diabetic will not be anxious, worried or hurried.

Free diets, as advocated and used at present, while the diabetic is receiving protamine zinc insulin, are prone to result in a harmful degree of glycosuria, polyuria and dehydration.

The publicized belief that all diabetics of long duration suffer from crippling complications is not substantiated in our experience. The avoid-

ance of polyuria (dehydration) and hypoglycemic reactions, and the maintenance of qualitative nutrition are the most effective means to combat the complications of diabetes.

BIBLIOGRAPHY

1. Joslin, E. P., Root, H. F., White, P., Marble, A., and Bailey, C. C.: The treatment of diabetes mellitus, 1946, Lea & Febiger, Philadelphia, pp. 68–80.
2. Barker, M. H., and Kirk, E. J.: Experimental edema (nephrosis) in dogs in relation to edema of renal origin in patients, Arch. Int. Med., 1930, xlv, 319–346.
   Allen, E. V., Barker, N. W., and Hines, E. A., Jr.: Peripheral vascular disease, 1946, W. B. Saunders Co., Philadelphia, p. 361.
3. Mosenthal, H. O., and Mark, M. F.: Advantages of protamine zinc insulin: Results in diabetes complicated by tuberculosis, Jr. Am. Med. Assoc., 1941, cxvi, 2652–2653.
4. Wilder, R. M.: Clinical investigations of insulins with prolonged activity, Ann. Int. Med., 1937, xi, 13–30.
   Tolstoi, E., and Weber, F. C., Jr.: Protamine zinc insulin: A metabolic study, Arch. Int. Med., 1939, lxiv, 91–104.
5. Lewis, L. A., Schneider, R. W., McCullagh, E. P., and Clark, J.: Tiselius electrophoresis studies of plasma proteins in diabetes mellitus, Jr. Clin. Endocrinol., 1944, iv, 535–539.
   Schneider, R. W., Lewis, L. A., and McCullagh, E. P.: Plasma proteins. I. Alteration in diabetic retinitis, Am. Jr. Med. Sci., 1946, ccxii, 462–465.
6. Allen, F. M.: Pathology of diabetes. IV. Role of hyperglycemia in production of hydropic degeneration of islands of Langerhans, Jr. Metab. Res., 1922, i, 75–88.
   Haist, R. E., Campbell, J., and Best, C. H.: The prevention of diabetes, New England Jr. Med., 1940, ccxxiii, 607–615.
   Lukens, F. D. W., and Dohan, F. C.: Pituitary diabetes in the cat; recovery following insulin or dietary treatment, Endocrinology, 1942, xxx, 175–202.
7. Brush, J. M.: Initial stabilization of the diabetic child, Am. Jr. Dis. Child., 1944, lxvii, 429–444.
8. Newburgh, L. H., and Conn, J. W.: A new interpretation of hyperglycemia in obese middle-aged persons, Jr. Am. Med. Assoc., 1939, cxii, 7–11.
   Newburgh, L. H.: Control of the hyperglycemia of obese "diabetics" by weight reduction, Ann. Int. Med., 1942, xvii, 935–942.
9. Ricketts, H. T., Brunschwig, A., and Knowlton, K.: Effects of total pancreatectomy in a patient with diabetes, Am. Jr. Med., 1946, i, 229–245.
10. Mosenthal, H. O.: Hyperglycemia: Evaluation in treatment of diabetes mellitus, Jr. Am. Med. Assoc., 1935, cv, 484.
    Bayne-Jones, Stanhope: The effects of carbohydrates on bacterial growth and development of infection, Bull. New York Acad. Med., 1936, xii, 278.
    Himwich, H. E.: Blood sugar in experimental diabetes, ibid., 1936, xii, 284.
    Tolstoi, Edward: Blood sugar in diabetes mellitus, ibid., 1936, xii, 295.
    Richardson, R.: Immunity in diabetes. III. Relation of tissue glycogen and blood chemistry to bacterial dissemination, antibody formation and survival after infection in diabetes, Jr. Clin. Invest., 1940, xix, 239–250.
11. Soskin, S., and Levine, R.: Carbohydrate metabolism, 1946, University of Chicago Press, Chicago, p. 185 and p. 253.
12. Baker, A. B.: Cerebral lesions in hypoglycemia. II. Some possibilities of irrevocable damage from insulin shock, Arch. Path., 1938, xxvi, 765–776. III. Experimental investigations, Arch. Path., 1939, xxviii, 298–305.
    Saks, A. L., and Alexander, L.: Fatal hypoglycemia: Clinicopathologic study, Arch. Neurol. and Psychiat., 1939, xlii, 286–297.

13. Dolger, H.: Clinical evaluation of vascular damage in diabetes mellitus, Jr. Am. Med. Assoc., 1947, cxxxiv, 1289–1291.
14. John, H. J.: The treatment of diabetes: Use of protamine and crystalline insulin, New York State Jr. Med., 1938, xxxviii, 1266.
Handelsman, M. B.: Variations in the response of diabetics to insulin therapy, New York State Jr. Med., 1943, xliii, 2287–2293.
Joslin, E. P., Root, H. F., White, P., Marble, A., and Bailey, C. C.: The treatment of diabetes mellitus, 1946, Lea & Febiger, Philadelphia, p. 348.
Anderson, G. E.: A creed for the treatment of diabetes, Am. Jr. Digest. Dis., 1947, xiv, 170–178.
15. Tolstoi, E., and Weber, F. C., Jr.: Protamine zinc insulin: A metabolic study, Arch. Int. Med., 1939, lxiv, 91. Protamine zinc insulin: A clinical study, Arch. Int. Med., 1940, lxvi, 670.
Tolstoi, E., Almy, T. P., and Toscani, V.: Treatment of diabetes mellitus with protamine insulin: Is a persistent glycosuria harmful? A metabolic study of a severe case, Ann. Int. Med., 1942, xvi, 893.
16. Mitchell, S. W.: On the production of cataract in frogs by the administration of sugar, Am. Jr. Med. Sci., 1860, xxxix, 106–110.
17. Aschoff, Ludwig, *in* Cowdry, E. V.: Arteriosclerosis, 1933, Macmillan Company, New York.

THE PROGNOSTIC SIGNIFICANCE OF THE "GUILLAIN-BARRÉ SYNDROME" *

By MORTON HAND, M.D., and MARTIN RUDOY, M.D., *Brooklyn, New York*

TWENTY years after the original description [1] of a clinical entity familiarly known as the Guillain-Barré syndrome, Guillain proposed to "delimit as exactly as possible" [2] the syndrome isolated in 1916, so that it might be "kept distinct from (the remainder of) the broad group of polyradicular neuritides with nonfatal outcome" which are seen quite often in neurological practice. In 1937, however, Guillain revoked his opinion of a year before without reservation. Nevertheless, it seems advisable to reaffirm Guillain's original position because wartime experience with a distinctive group of cases appears to bear out his original contention that the disease can be "delimited." Furthermore, it appears necessary so to delimit this syndrome in order to avoid confusing it with related conditions.

The advantages of such clinical isolation are facilitation of the study of etiological factors, of the course of the disease, of its response to treatment, of the incidence of serious complications and of the prognosis. Although nosologic considerations are not the aim of such delimitation, their importance in the analysis of factors which will yield additional knowledge of the disease is recognized.

This presentation will describe the occurrence of remissions and exacerbations in this disease, such remissions and exacerbations having been considered unusual in inflammatory disease of the nervous system. Etiologic relationships with throat infections such as tonsillitis, exudative pharyngitis of streptococcic or diphtheritic origin, and pyemia will be apparent. Evidence is presented which suggests that the sulfonamides used in treatment of these primary infectious conditions may on occasion constitute the etiological agent in the neurologic syndrome.

That involvement of the "final common pathway" often accounts for "bulbar" and "bladder" disturbances which in this series were not indisputably due to implication of the central nervous system is obvious. The central nervous system may be involved, but clinically such implication is masked by disturbance of peripheral nerves, so that involvement from cerebral cortex to spinal cord pathways may be predicated but not proved.

The occurrence of albumino-cytologic dissociation in this syndrome and not in other inflammatory diseases of the nervous system has not been explained.[3, 4, 5, 6] This laboratory finding is the prominent differentiating feature of the disease. Conditions in which disturbance of the nervous system are due to toxins show little or no alteration in total protein content of the cerebrospinal fluid.

* Received for publication June 2, 1947.
From the Neuropsychiatric Service of the 37th General Hospital.

Most of the cases occurring among American troops were not seen at the onset of their illness. They came under observation several weeks after the onset of the "paralytic" stage and several were followed to complete recovery, including two patients who were returned to duty. None of the patients died or were left with disabling residua.

Cases occurring in German troops gave evidence of progressive improvement. None was seen at the onset of illness and the laboratory data obtained earlier in their illness were obtained from German hospital records. The findings were discussed with German Medical Officers who regarded them as accurate and reliable.

Two cases seen on the neurological service of Kings County Hospital, Brooklyn, New York, are briefly described in order to compare them with cases seen abroad in military service and to note their similarity.

Case Reports

Case 1. The first case illustrates the typical symptom complex with remissions and exacerbations.

A 23 year old soldier stated that he had suffered an attack of tonsillitis on October 5, 1943. Throat smears on October 9 and October 16 revealed no diphtheria bacilli.

On October 22, 1943 the patient experienced swallowing difficulty which progressed so that, on admission to the hospital, he was unable to swallow without gagging or returning fluid through his nose. The voice had a nasal twang, the palate was weak, and there was evidence of recent weight loss. The spinal fluid protein was 64.8 mg. per cent; and no cells were observed. Examination was otherwise negative. The patient was tube-fed for two weeks and recovered "bulbar" control. On December 1, 1943 he complained of general weakness and visual disturbance and again of difficulty in swallowing. The tendon, abdominal and cremasteric reflexes were not obtained. Moderate weakness of all extremities and slight flattening of the right side of the face were noted. There were no sensory alterations. On December 4 these signs were noted together with loss of muscle, joint, tendon and vibratory sensibility in the lower extremities. The spinal fluid protein was 98 mg. per cent. The intensity of weakness increased, and by December 13, 1943 the patient again had to be tube-fed. There was diffuse and severe atrophy of all muscles of the extremities, and of the temporal, rectus capitis, sternomastoid, trapezius and paravertebral muscles on both sides. The tongue was atrophied, and there was bilateral facial weakness. The patient was unable to hold his head erect, sit, move his jaws, chew, swallow, speak above a whisper, or move his extremities. It was necessary to suction mucus from the pharynx and change his position repeatedly for more than a week. He then began to regain his strength.

By December 21 he was able to speak with moderate vocal resonance. Position and vibratory sensibility remained impaired. Painful and thermal stimuli were not perceived distally in all four extremities. By December 28, there was additional improvement in muscular strength in the extremities but a loss of all modalities of sensation in the upper extremities was now noted. There was return of power of the pharyngeal muscles but tube feeding was still necessary. Weakness of the extraocular muscles kept the eyeballs immobile.

By January 15, 1944 swallowing difficulty had ceased and motor power improved in the arms, so that the patient could lift his arms and flex his elbows. Wrist and foot drop were bilaterally present. The voice was normal. There was considerable

return of sensibility in the extremities, but the patient complained of burning sensations in his legs. The atrophy and areflexia persisted. Spinal fluid protein was 117.9 mg. per cent. During February and March 1944, there occurred progressive improvement in motor power and muscle volume. All modalities of sensation improved but vibratory sensibility continued to be somewhat impaired. At the time of transfer to a hospital in the United States, the patient was able to stand and walk and the tendon jerks were present, but weak and exhaustible. He continued to complain of burning sensations in the hands and feet. Laboratory studies at this time revealed a normal electrocardiogram, blood and spinal fluid. The spinal Wassermann reaction was negative.

Case 2. This case showed progressive muscular involvement with exacerbations. The patient, a 22 year old soldier, stated that he "had a cold" on November 27, 1943, and two days later experienced numbness in his toes and legs which spread to his body, then to his finger tips and arms. The tongue began to feel numb, he lost the sense of taste, had difficulty in swallowing, and regurgitated fluid through the nose. On December 3, 1943 he experienced blurring of vision and diplopia. He stated that he could walk well until January 10, 1944. When examined on January 18 he was bedridden, emaciated, and required tube feeding. He spoke hoarsely with a nasal twang and exhibited slight bilateral facial weakness. The muscles of the pharynx were paralyzed and its mucosa was insensitive. The patient could neither hold his head erect nor turn it from side to side. The tongue appeared normal. Motor power of all four extremities was weak, the muscles appearing shrunken and atrophied. Tendon jerks in the upper and lower extremities, and cremasteric and abdominal reflexes could not be elicited. A left Babinski response was produced. Pin prick and cotton touch perception were diminished throughout the body, especially in the perioral, perianal, genital areas and in the distal portions of the extremities. Vibration was not perceived over the extremities. All laboratory studies were negative except for the finding of 76.4 mg. per cent of total protein in the cerebrospinal fluid.

Because of pharyngeal weakness, the patient had difficulty in expectoration and aspirated mucus. On January 22, 1944 atelectasis of the right lung was noted when the patient suddenly became comatose, cyanotic and dyspneic. Bronchoscopic aspiration followed by stimulant drugs, oxygen by nasal catheter, and postural drainage were required as immediate lifesaving measures. From that date there was progressive improvement. Muscle power returned slowly and all modalities of sensibility progressively improved. At the end of March, 1944 the patient was free of swallowing difficulties and could walk quite well. However, although the abdominal and cremasteric reflexes were elicited, no tendon reflexes could be obtained, and the Babinski sign on the left persisted.

Case 3. The patient was a 34 year old soldier who developed a sore throat on November 7, 1943 and was ill for two weeks. During this period there was an exudate on the soft palate and on the left tonsil. Smears examined for the diphtheria bacillus were negative. Sulfadiazine was administered from November 11, 1943 to November 27, 1943, but was discontinued when the patient began to complain of precordial pain. On December 7, 1943 he developed numbness of the face, lips, fingers and toes. He "lost" his voice, had difficulty in swallowing, regurgitated fluid through the nose, and suffered "blurring of vision." At this time examination disclosed diminished motor power in all extremities, diminished tendon jerks at the elbows, ankles and knees, and diminished sensitivity to touch and pin prick on the tongue and in all four extremities. On January 13, 1944 there was loss of vibratory and position sensibility of all extremities, marked weakness of the muscles of the extremities and trunk, and loss of weight. There was also imperception of urination, facial weakness on the right, loss of touch and taste sensation of the tongue and buccal mucosa. A right Babinski sign was present.

Laboratory examinations showed normal findings except for the cerebrospinal fluid which had a total protein content of 74.7 mg. per cent with no cells.

Weakness persisted during the next six weeks except for a slight return of power in the lower extremities. The deep tendon reflexes were not elicited, and atrophy of the extremities with loss of sensation was noted at the time of transfer.

Case 4. The patient was a young infantry soldier who had a sore throat early in November of 1943. On November 16, 1943 he noted stiffness, weakness and sharp pains in the legs, and difficulty in walking. He was given routine tetanus toxoid and a typhoid vaccine injection on this date along with the other members of his unit. His complaints continued and on November 20, 1943 he was hospitalized. Examination disclosed blurred optic disc margins bilaterally, unobtainable tendon reflexes at the elbows, ankles and knees, flaccid paralysis of the lower extremities, marked weakness of the upper extremities more severe distally, atrophy of the musculature of the extremities, and diminution to absence of all modalities of sensibility in the extremities, more severe distally.

An increase in motor power occurred during hospitalization so that by January 21, 1944 the patient could sit up, move his legs, and use his arms. There was some return of pain and temperature sensibility but vibratory and joint position sensibility continued diminished.

Laboratory findings. Cerebrospinal fluid total protein: November 30, 1943—310 mg. per cent, December 8, 1943—338 mg. per cent, January 13, 1944—156.8 mg. per cent. Electrocardiograph, December 1943, indicated slight myocardial damage on the basis of "abnormal" T-waves and sinus tachycardia. There was gradual restoration of power and sensation so that the patient was walking normally at the time of transfer and had only slightly diminished sensation in all modalities.

Case 5. The patient was a 24 year old soldier who had an attack of tonsillitis with a white patchy pharyngeal exudate in October of 1943. One month later he noticed numbness and shooting pains in the legs which increased until November 20, 1943, when he had difficulty in balance while walking. He began to regurgitate fluid through his nose when swallowing. When he was hospitalized on January 3, 1944 he complained of numbness of fingers and feet, and said that his legs "felt like wood." He had lost 20 pounds in two months and slapped his feet when he walked. Examination revealed blurring of the optic discs bilaterally, diminution of all modalities of sensation in the distal portions of the extremities, atrophy of the muscles of the trunk and extremities, unobtainable tendon reflexes at the elbow, knee and ankle joints, and no abdominal or cremasteric reflexes.

Laboratory studies revealed cerebrospinal fluid total protein of 66.1 mg. per cent on January 13. There was gradual improvement in muscle tone and strength so that by April 1944, the patient walked fairly well. The tendon reflexes were present but weak at that time. There still remained evidence of impairment of joint position and vibratory sensibility in the legs.

The following case illustrates an exacerbation of symptoms after partial recovery.

Case 6. The patient was a 25 year old soldier who had "Sandfly fever" on August 14, 1944. He complained of headaches, general malaise and fever. On August 17 he was hospitalized because of weakness and numbness of the extremities, paralysis of the facial muscles, and difficulty in swallowing. During the next five days he improved. He was able to walk and had no difficulty in swallowing. On August 22 he suddenly collapsed while walking and gradually became weaker. He complained of blurring of vision and inability to feel his legs. On August 27 a pink macular rash appeared on his chest, abdomen and arms. He was unable to move his eyes and he had a bilateral lid ptosis with facial diplegia and a weak, trembly voice. Examination

revealed loss of all modalities of sensation in all four extremities distally to the elbows and knees, and unobtainable tendon jerks at the elbows, knees and ankles.

There was gradual but asymmetrical improvement from this time until November 28, 1944, when he was transferred. At this time he presented weakness of both lower extremities, and loss of pain sensibility on the left side of the face and on both feet and hands, paresis of the left side of the face, absent tendon jerks at the elbows, knees and ankles. The cerebrospinal fluid on August 14 revealed a total protein of 70 mg. per cent; 246 mg. per cent August 28, 1944, 114.6 mg. per cent September 10, 1944, 149.25 mg. per cent October 25, 1944, 160 mg. per cent November 20, 1944.

Case 7. The patient was a 30 year old Sergeant who suffered from boils in both axillae in November 1944. He received 60 injections of penicillin in December 1944 and during this period he suffered from a severe sore throat. On January 10, 1945 he noted weakness of his extremities, awkwardness in gait, clumsiness of his hands and fingers, and blurring of vision. His speech became thick and hoarse, his lips and tongue became insensitive. He was admitted to the hospital on February 17, 1945. Examination revealed weakness and loss of fine movements in the extremities, absent tendon jerks at the elbows, knees, and ankles. The left cremasteric and abdominal reflexes were not elicited. Pin prick was poorly perceived distally in all four extremities, more so on the left. Laboratory examination revealed only an elevated total protein in the cerebrospinal fluid of 78 mg. per cent on February 17, 1945.

Case 8. A 41 year old soldier entered the hospital for dermatitis January 4, 1945, and on January 17, 1945 developed a non-diphtheritic exudative tonsillitis which soon subsided. On February 16, 1945 he noticed that his left eye "watered" and several days afterward the left side of his face became "weak." He then developed progressive numbness of the hands and feet and arms and legs. His penis felt numb and the urinary stream "lost force." He became constipated and had "sore muscles." He began to suffer difficulty in swallowing and speaking clearly and he staggered while walking, losing his balance when arising from sitting positions. His hands became clumsy. Examination revealed weakness in all extremities, absent tendon jerks at the knees and ankles, diminished sensibility to pin prick, touch, vibration and change of position in all four extremities, more marked distally. The spinal fluid total protein was 51 mg. per cent on February 26, 1945, and 76.8 mg. per cent on March 7, 1945. Improvement was gradual until the time of transfer on April 25, 1945. At that time he was able to walk and had fair use of his hands and fingers with return of sensibility in the hands and feet.

Case 9. A 32 year old soldier with a chronic anxiety state complained of weakness, stiffness and numbness of the extremities which began one month after the onset of a "diphtheritic" sore throat in May of 1944. At this time he had difficulty in swallowing. His "food stuck in his throat and he talked through his nose." When he was hospitalized for these complaints on June 6, 1944, he presented a nasal twang, weakness, areflexia and diminished sensibility in all extremities. All throat smears were negative for diphtheria. From June 10 to July 4, 1944 his weakness increased so that he became bedridden. Thereafter improvement in power and sensibility was progressive until the middle of August when the reflexes began to return and sensibility increased. He was discharged to duty September 10, 1944 with normal reflexes and no sensory disturbances. Six weeks later he was returned to the hospital because of his chronic anxiety state. At this time the reflexes were 2-plus, there were no complaints of weakness or numbness of the extremities, and no sensory impairment was noted. Spinal fluid studies revealed total protein of 136 mg. per cent on June 12, 78.5 mg. per cent on July 14, 1944.

Case 10. A 29 year old Lieutenant entered the hospital on June 28, 1944 for tonsillitis from which he recovered. On July 11, 1944 tonsillectomy was performed. He was seen on the neurological service for the first time on July 16, 1944 because he had reported numbness of the hands. At this time he stated that on May 4, 1944

he had had a sore throat and saw white patches in the pharynx upon looking into the mirror. He had had similar sore throats one year previously in Sicily and on frequent occasions since the age of eight before entering military service.

On May 4 he noted weak and numb feelings in all extremities. On June 7 he regurgitated fluids through the nose and his throat felt numb. He found that he was unable to taste food and his speech was indistinct. On June 20 he stumbled and staggered but the numbness of the throat had subsided and his speech had improved. He no longer regurgitated and numbness was not felt in the upper extremities, although it persisted in the lowers.

Examination revealed that the patient waddled and stumbled while walking. He used his hands awkwardly in fastening and unfastening his clothing. The speech was muffled. The gag reflex was present. The tendon reflexes were not obtained. The abdominal and cremasteric reflexes were present but weak and exhaustible. Power was diminished about 25 per cent at al' joints. Light touch, pain and thermal sensibility were easily perceived throughout the skin areas. Bathydysesthesia was present in the feet and hands. The spinal fluid was clear, contained 2 cells per cu. mm., 75.5 mg. per cent glucose, and 73.1 mg. per cent total protein.

Two weeks later the patient stated that he felt better but had fallen on several occasions when he went to the latrine or mess hall. His "voice tired quickly" and paresthesia was no longer experienced in the pharynx or extremities. The clinical signs were unaltered. Over a period of two weeks power rapidly diminished in all extremities so that he was unable to feed himself or alter the position of the extremities or trunk in bed. The clinical signs were unaltered except for greater loss of power. The spinal protein was 49.7 mg. per cent on August 18. By the end of August power had begun to return in all extremities. On the last of September when he returned to duty at his own request, the only complaint was "tiring of the hips after walking a couple of miles." The reflexes were not obtained at this time and all modalities of sensibility were slightly diminished in the distal portions of the extremities.

The patient returned for examination on November 10, 1944, after "hiking all over Italy." He stated that he still "felt it in the hips" after climbing hills. The reflexes were 2-plus throughout, and sensibility was slightly impaired in the toes. Motor power appeared normal at all joints and no atrophy was noted in the hip muscles.

Case 11. A 20 year old soldier developed weakness and paresthesia of the extremities, retention of urine, constipation, muscular pains, and mild difficulty in swallowing in October 1944. The deep reflexes were not obtained and all modalities of sensibility were diminished in all extremities. Total protein in the spinal fluid varied from 85 to 160 mg. per cent during the six weeks he was observed. There was some return of power and sensibility at the time of evacuation from Italy but he was bedridden when transferred.

In the following five cases the appearance of the neurological symptoms followed clinical diphtheria.

Case 12. The onset of swallowing difficulties, weakness of the extremities and paresthesias occurred one month after pharyngeal diphtheria. There was diminished power and areflexia in all four extremities, diminished sensibility in all modalities in the distal portions of the extremities, perioral and perianal regions. Spinal fluid protein was 45.3 mg. per cent and 58.8 mg. per cent. Sensibility returned and power was gradually increasing at the time of transfer, three months later.

Case 13. Three months after an attack of pharyngeal diphtheria this patient suffered accommodation difficulty and weakness of the extremities. There was diminished sensibility of the hands and feet and unobtainable tendon reflexes. Spinal

fluid total protein was 68.2 mg. per cent. Gradual improvement in power and sensibility occurred during two months' observation until the time of transfer.

Case 14. Pharyngeal diphtheria in December 1944 was followed in three weeks by difficulty in enunciation and swallowing. Five weeks later paresthesias and weakness in all extremities occurred. There was diminished vibratory sensibility in the hands and feet and areflexia on examination five months after onset. Power was diminished but improving. Spinal fluid total protein was 28.2 mg. per cent.

Case 15. The patient suffered a diphtheritic sore throat and two weeks later noted difficulty in visual accommodation. There was progressive involvement of the extremities by diminished sensibility in all modalities and diminution of tendon jerks. Spinal fluid total protein was 44.5 mg. per cent. Gradual return of sensibility and power occurred in four months.

Case 16. The patient had a pharyngeal diphtheritic infection on January 2, 1945. On January 22, 1945 he noted difficulty in accommodation. On February 8, 1945 he presented complaints referable to swallowing and speech and weakness of the arms and legs. Examination revealed areflexia at the elbows, knees and ankles and diminished sensibility in all modalities in all four extremities. Spinal fluid total protein was 38.6 mg. per cent in March, 1945 and 37.4 mg. per cent in June, 1945. Progressive improvement in power and sensibility occurred during three months to the time of transfer.

The following four cases occurred in association with large (self prescribed) dosage of sulfonamides.

Case 17. This patient developed weakness and paresthesias of the extremities two weeks after unlimited use of sulfonamide drugs. There occurred areflexia, and diminution of all modalities of sensation in the extremities, confinement to bed for three months, and gradual recovery in six months. Spinal fluid total protein was 32 mg. per cent during the period of greatest disability.

Case 18. Two months after unlimited dosage with sulfonamide drugs the patient developed weakness, areflexia, paresthesias and diminished sensibility in the extremities. Gradual recovery was noted in five months. Total protein in the spinal fluid was 29.6 mg. per cent during the period of greatest disability.

Case 19. Six weeks after unlimited dosage with sulfonamide drugs the patient developed weakness, areflexia and diminished sensibility in all extremities. Total protein in spinal fluid was 23.0 mg. per cent in May of 1945 and 45.0 mg. per cent in June, during the period of greatest disability. Gradual improvement occurred during July and August.

Case 20. Two weeks after unlimited ingestion of sulfonamides this patient developed areflexia, marked weakness, diminished sensibility in all modalities in all extremities. Total protein in the spinal fluid was 32 mg. per cent during the period of greatest disability. Gradual recovery was observed during a three month period.

Case 21. This patient developed weakness and clumsiness of the extremities one month after a severe sore throat. He suffered diminution of sensibility in all modalities in the extremities and there was areflexia at the elbows, knees, and ankles. Spinal fluid total protein was 160 mg. per cent. Gradual improvement occurred over a period of two months so that he was able to walk when discharged, though he still presented areflexia and sensory disturbances in the hands and feet.

Case 22. This 19 year old girl developed pyodermia on February 15, 1946 and was treated with penicillin. On February 25, 1946 she noted difficulty in accommodation. On April 11, 1946 she suffered weakness of all extremities and numbness and diminished sensibility in all modalities in all four extremities. There was imperception of urination. On May 9, 1946 she had difficulty in speech and swallowing and increased weakness of her limbs so that she became bedridden. From that point she

improved progressively to complete recovery in July 1946. Spinal fluid protein was 125 mg. per cent April 13, 1946; 126 mg. per cent May 1; 173 mg. per cent May 18; 101 mg. per cent on June 8, 1946; and 40 mg. per cent on July 10, 1946.

Comment

Among the 11 cases of American soldiers with polyneuritis there were 10 who had a definite history of pharyngitis, six with an exudate, which preceded the onset of neurological disturbance by three to six weeks. All were characterized by diminution of motor power, reflexes and sensibility in the extremities. Accommodation and swallowing difficulties were common at the onset and some urinary disturbances were noted. Elevation of the total protein content of the spinal fluid without increase of cells was present in every case. Five cases of polyneuritis were seen among German prisoners of war whose throat smears revealed the presence of the diphtheria bacillus. In these patients the total protein of the spinal fluid was normal or only very slightly elevated. Similarly, in the four German prisoners with polyneuritis associated with extraordinary ingestion of sulfonamides over a long period there was no elevation of the total protein level in the spinal fluid.

Fever was not present in any of the cases in association with the neurological disability but was present in rare instances at the time of throat infection weeks before. Spontaneous pains or burning sensations occurred but were not common in this series.

In general the total protein level in the spinal fluid was high at the height of the symptomatology and decreased as the signs and symptoms of polyneuritis subsided. The first evidence of progressive recovery usually occurred two or three months after the onset. Few of the patients appeared acutely ill, but severe motor disability confined many to bed in a helpless state, and complications resulting from palatal paralysis and swallowing difficulty threatened life in two instances.

Treatment consisted of bed rest, physiotherapy from the onset of motor weakness, thiamine chloride 300 mg. daily with a high vitamin diet. Activity was permitted to the extent of the patient's capability. This was an adjunct to the physiotherapy and had as its aim the prevention of muscular deterioration.

The pattern of the disease may be described as follows: Following recovery from a suppurative sore throat, exudative skin lesion, purulent skin or lymph node infection there occurs a rather sudden onset of weakness and numbness of the extremities after a latent period of several days or weeks. With the disability in the limbs there is often disturbance in visual accommodation and in swallowing. The facial muscles may become paralyzed, and then there may occur progressively increasing involvement of sensibility and motor power, first in the extremities then in the trunk. Occasionally, because of imperception of urination there may be dribbling or retention. Some improvement may occur, following which a sudden relapse may render

the patient helplessly bedridden. The course is afebrile throughout and the prognosis for complete recovery excellent.

Gordon Holmes [7] in 1917 described a group of cases among soldiers which gave no evidence of cerebrospinal fluid changes. He called the disease acute febrile polyneuritis. In 1918, Brandford, Bashford and Wilson [8] described cases under the same classification and in their series the spinal fluid was also normal. In 1919 Casamajor [9] and Kennedy [10] described a similar disease picture. The syndrome encountered in this series among American patients both abroad and in the United States was described recently in illustrative case presentation by Mackay,[11] by pathologicoanatomic studies intended to determine the etiological agent by Lassen, Ipsen and Bang,[12] by Lewey,[13] and by Lowenberg and Foster.[14] As mentioned above, the original description by Guillain, Barré and Strohl [1] corresponded with the conditions observed in this series.

The comprehensive review by DeJong [15] probably includes related though separate syndromes from that seen in this group of patients, since it described cases in which the entire nervous system was generally involved. Among our patients no definite clinical evidence of other than peripheral nerve and nerve root involvement was obtained. Cases in which peripheral nerves from the brain stem were involved in several of our patients represented the most serious of the entire series.

The cases occurring among American soldiers and civilians were considered to be caused by a toxic or infectious agent. Since practically every case was preceded by some throat infection (table 1) followed by a variable but limited latent period (table 2), the infection was predicated as instrumental in the cause of the neuropathy. Vitamin deficiency was eliminated as a possible causal factor since all patients had a history of a diet superabundant in vitamins, and although vitamins were administered, no definite improvement could be ascribed to such therapy.

In its third report, the Matheson Commission [16] suggested that the Guillain-Barré syndrome may be a virus disease allied to epidemic encephalitis

TABLE I

Preceding Infections

	German	American
1. Cold or sore throat before onset	1	4
2. Membrane or exudate in throat before onset	3	5
3. Skin or lymph node infection before onset	1	1
4. Other	3 (Gonorrhea)	1 Sandfly fever

TABLE II

Incubation Period after "Predisposing" Infection or Medication

	German	American
1–7 days	1	2
7–21 days	6	5
21 days or more	1	5
Unknown	1	1

TABLE III

Chief Symptoms and Signs

	German	American
Swallowing difficulty	2	8
Visual accommodation difficulty	4	5
Weakness and numbness of extremities	6	8
Sphincteric disturbances	0	2
Babinski positive	0	2
Myocardial involvement	1	1
Facial palsy	0	4
Pains sharp or shooting	0	3
Muscle tenderness	0	1
Muscle atrophy	1	4
Palatal paralysis	3	5
Absent deep reflexes	7	12
Diminished sensibility in the extremities	5	12

lethargica. Barker, Cross and Irwin,[17] and Beriel and Devic [18] believed that polyradiculoneuritis ought not to be considered a peripheral form of epidemic encephalitis. Guillain's [2] conception was similar. Barré [19] suggested an as yet unknown organism or virus.

No pathological material was obtained in our cases since all recovered. Guillain and Barré's cases also recovered. DeJong's review [15] reported the pathological findings of several investigators. No consistency in the findings was noted, however. Hecht [20] and Taylor and McDonald [21] described lesions in the gray matter of the spinal cord and cerebral hemispheres and the latter report described the changes as inflammatory in nature. Gilpin, Moersch and Kernohan [22] saw no evidence of inflammation. The changes they observed were degenerative and most marked in the peripheral nerves with slight spinal cord involvement, particularly in the anterior horns of the gray matter. The predominant alteration was edema with myelin degeneration and fragmentation of the axis cylinders in the peripheral nerves. Barker,[23] Alajuanine,[24] Garvey and Slavin,[5] and others suggested that the pathology might be due to inflammation of the sheath of Schwann where there occurs an increase in the number and volume of the sheath cells with diffuse lymphocytic infiltration of the nerve roots, peripheral nerves and of the myelin sheath. They believed that the responsible agent was a filtrable virus. There is, therefore, no general agreement as to the underlying pathological changes. Most workers described degenerative changes involving the nerve roots and peripheral nerves and secondary degenerative alteration in the anterior horn cells. No definite evidence of inflammatory reaction has been shown either in the nerve, nerve root, meninges, gray matter of the spinal cord, or in myelin sheaths. Furthermore, there is no evidence of glial proliferation or infiltration within the spinal cord.

In considering the differential diagnosis, the sudden occurrence of flaccid paralysis sometimes occurring with muscle tenderness and meningeal irritation may suggest anterior poliomyelitis. The minimal febrile reaction, symmetry of limb involvement, and the occurrence of subjective and objective sensory change differentiate the syndrome clinically. The spinal fluid

findings offer definite diagnostic evidence. Heavy metal poisoning and neuritis with avitaminosis can be ruled out by the clinical course, spinal fluid findings, absence of response to vitamin therapy or of history of exposure to the metals.

As has been shown in this presentation, however, post-diphtheritic neuritis closely resembles the Guillain-Barré syndrome. Differentiation depends on demonstration of the diphtheria bacilli and on the relatively slight elevation of spinal fluid total protein.

Since the etiology is unknown, treatment has been palliative and empirical, and no specific measures are applicable. The use of thiamine chloride, early application of physiotherapy, and fever therapy in order to reduce the period of disability and shorten convalescence have been suggested by Straus and Rabiner.[25] Most important is the prevention of complications due to swallowing difficulty and bladder dysfunction, such as aspiration pneumonia, asphyxia, atelectasis, or ascending urinary infection. Since the disease seems to be self limited, the patients improve despite lack of specific treatment. However, death was narrowly avoided in two cases of this series. It may be possible to avoid fatalities by zealously watching all cases with swallowing or respiratory difficulty and providing apparatus for tube feeding, artificial respiration and bronchoscopy for possible emergencies in these patients. The fatal cases described by DeJong [15] were due to "bulbar" and "diaphragmatic" failure. Those presented here had "bulbar nerve" paresis both motor and sensory. They required suction and tube feeding. They complained of facial and perioral anesthesia and paresthesia. Perhaps because the lesions were not within the brain stem these cases could be successfully tided over the paralytic phase by unremitting nursing care. In true bulbar involvement which probably did not occur in the syndrome described in this presentation, such measures usually fail. DeJong [15] reported changes in the motor nuclei in the medulla and anterior horn cells in two cases with fatal outcome. Gilpin, Moersch and Kernohan [22] found no abnormalities in the anterior horn cells, brain stem, cerebellum, basal ganglia or cerebral hemispheres, but did find degenerative changes in the peripheral nerves including the peripheral portions of the cranial nerves. The cases in both reports were clinically comparable. It is likely that many cases with symptoms of "bulbar" involvement are explainable on the basis of disease in the peripheral nerves emanating from nuclei in the brain stem.

BIBLIOGRAPHY

1. Guillain, Georges, Barré, J. A., and Strohl, A.: Sur un syndrome de radiculo-né vrité avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire; remarque sur le caractères cliniques et graphiques des reflexes tendineux, Bull. et mém. Soc. méd. de hôp. de Paris, 1916, xl, 1462.
2. Guillain, Georges: Radicular neuritis with acellular hyperalbuminosis of the cerebrospinal fluid, Arch. Neurol. and Psychiat., 1936, xxxvi, 975.
3. Merritt, H. H., and Fremont-Smith, F.: The cerebrospinal fluid, 1937, W. B. Saunders Company, Philadelphia, pages 180–185.

4. Pinckney, C.: Acute infective polyneuritis, Brit. Med. Jr., 1936, ii, 333.
5. Garvey, P. H., and Slavin, H. B.: Acute infectious polyneuritis, Internat. Clin., 1938, iv, 38.
6. Collier, J.: Peripheral neuritis, Edinburgh Med. Jr., 1932, xxxix, 601.
7. Holmes, Gordon: Acute febrile polyneuritis, Brit. Med. Jr., 1917, ii, 37.
8. Bradford, J. R., Bashford, E. F., and Wilson, J. A.: Acute infective polyneuritis, Quart. Jr. Med., 1918, xii, 88.
9. Casamajor, Louis: Acute ascending paralysis among troops: pathologic findings, Arch. Neurol. and Psychiat., 1919, ii, 605.
10. Kennedy, F.: Infective neuronitis, Arch. Neurol. and Psychiat., 1919, ii, 621.
11. Mackay, Roland P.: Acute encephalo-myelo-radiculoneuritis (Guillain-Barré syndrome), Med. Clin. N. Am., 1945, 1–8.
12. Lassen, H. C. A., Ipsen, J., and Bang, J.: Etiological studies on acute polyradiculitis of the Landry type—experiments on the demonstration of a virus with negative outcome, Acta med. Scand., 1943, cxv, 193.
13. Lewey, F. H.: What is the Guillain Barré syndrome? A study of the underlying pathological lesions, Jr. Pediat., 1945, i, 166.
14. Lowenberg, K., and Foster, D. B.: Polyradiculoneuritis with albuminocytologic dissociation; patho-anatomic report of 3 cases, Arch. Neurol. and Psychiat., 1945, liii, 185–190.
15. DeJong, R. N.: The Guillain Barré syndrome—polyradiculitis with albumino cytologic dissociation, Arch. Neurol. and Psychiat., 1940, xliv, 1068.
16. Report of the Matheson Commission—Epidemic encephalitis, etiology, epidemiology, treatment, 1939, Columbia University Press, New York, pp. 44–47.
17. Barker, L. F., Cross, E. S., and Irwin, S. V.: On the epidemic acute and subacute nonsuppurative inflammations of the nervous system prevalent in the United States in 1918–1919—encephalitis, encephalomyelitis, polyneuritis and meningo-encephalitis, Am. Jr. Med. Sci., 1920, clix, 157.
18. Beriel, L., and Devic, A.: Les formes "péripheriques" de l'encephalite epidemique, Presse méd., 1925, xxxiii, 1441.
19. Barré, J. A.: Considérationes diverse sur le syndrome de polyradiculonervite avec dissociation albumino-cytologique, Jr. Belge de Neurol. et de Psychiat., 1938, xxxviii, 313.
20. Hecht, M. S.: Acute infective polyneuritis in childhood, Jr. Pediat., 1937, xi, 743.
21. Taylor, E. W., and McDonald, C. A.: The syndrome of polyneuritis with facial diplegia, Arch. Neurol. and Psychiat., 1942, xxvii, 79.
22. Gilpin, S. F., Moersch, F. P., and Kernohan, J. W.: Polyneuritis, a clinical and pathological study of a special group of cases frequently referred to as instances of neuronitis, Arch. Neurol. and Psychiat., 1936, xxxv, 937.
23. Barker, L. F.: Acute diffuse (cerebral and spinal) polyradiculoneuritis following oral sepsis, Arch. Neurol. and Psychiat., 1934, xxxi, 837.
24. Alajuanine, T., Thurel, R., Hornet, T., and Boudin, G.: La polyradiculonervité aigue généralisée avec diplégic faciale et paralysie terminale des muscles respiratoires et avec dissociation albumino-cytologique, Rev. Neurol. and Psychiat., 1936, i, 681.
25. Straus, J., and Rabiner, A. M.: Myeloradiculitis—A clinical report of 7 cases, Arch. Neurol. and Psychiat., 1930, xxiii, 40.

MENINGITIS DUE TO *PSEUDOMONAS PYOCYANEA:* A REPORT OF THREE CASES TREATED SUCCESSFULLY WITH STREPTOMYCIN AND SULFADIAZINE *

By Louis Weinstein and Thomas S. Perrin, *Boston, Massachusetts*

Infections of the meninges with *Pseudomonas pyocyanea* (*Pseudomonas aeruginosa*) are distinctly uncommon but cannot be dismissed as unimportant because they have a high mortality rate, and constitute a serious risk in any procedure involving penetration of the membranes surrounding the brain or spinal cord. Stanley,[1] in a recent review of the literature, collected 41 cases of primary *Ps. pyocyanea* meningitis and 28 additional instances in which this disease appeared to be secondary to a focus elsewhere. To the latter type he added one case of his own. Of the group of primary meningitides, 78 per cent occurred as a result of the introduction of organisms during spinal puncture for diagnostic purposes or the instillation of contaminated anesthetic or other drug solutions into the subarachnoid space. Four individuals in whom this type of meningeal infection occurred during the course of intrathecal penicillin therapy for pneumococcal meningitis have been described by Harris et al.[2] Cairns and his co-workers have added descriptions of three more instances of meningitis due to this organism to the literature and Merwarth et al.[4] have contributed another. Three patients with *Ps. pyocyanea* meningitis were studied by Paine et al.[5, 6] and another case has been reported by DeBakey and Pulaski.[7] There are in the literature, therefore, a total of at least 82 reported instances of infection of the meninges with *Ps. pyocyanea.*

Treatment of *Ps. pyocyanea* has been uncertain and, on the whole, unsatisfactory. Harris et al. have reviewed the results of the use of sulfonamides and penicillin in this disease and found that of 21 cases treated with these drugs 15 (71.5 per cent) died.

Streptomycin has been shown to be inhibitory for *Ps. pyocyanea* in concentrations varying from 2 to 200 micrograms per ml. Most strains fail to grow in 8 to 50 micrograms per ml,[8] however, and, therefore, are susceptible to levels of this drug which are obtainable in the spinal fluid with generally accepted intrathecal doses.

A total of nine cases of *Ps. pyocyanea* meningitis treated with streptomycin have been reported in the literature (table 1). Of this group five died, a mortality rate of 55.5 per cent. The first case reported by Paine et al. (Case 1) was given intramuscular and intrathecal penicillin and oral

* Received for publication November 4, 1947.

From the Haynes Memorial and Evans Memorial, Massachusetts Memorial Hospitals and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

TABLE I

Meningitis Due to *B. pyocyaneus*, Streptomycin Treated

Case No.	Author	Age	Primary Condition	Presumed Mode of Infection	Amount of Single Dose of Streptomycin	Total Dose of Streptomycin	Additional Treatment	Course of the Disease	Outcome
1	Paine et al.	14	Epileptic seizure	Lumbar puncture	IT = 0.05 gm. IM = 1.0 gm.	IT = 0.45 gm. IM = 28 gm.	Sulfadiazine and IM penicillin	Rapid improvement	Recovered
2	Paine et al.	11 days	Congenital meningocele	Débridement of meningocele	IV = 0.25 gm.	IV = .55 gm. IM = 6.5 gm.	Penicillin IM and IT	Gradual improvement	Recovered
3	Paine and Finland	?	?	?	?	?	?	?	Died
4	Cairns et al.	?	Lateral sinus thrombosis, cerebral and cerebellar abscess	Cerebellar decomposition	IV = 80,000 units	IV = 620,000 units	Sulfonamides, penicillin	Unaffected	Died
5	Cairns et al.	?	Gunshot wound of neck	Wound infection	IV = 100,000 units IT = 100,000 units	IV = 210,000 units IT = 100,000 units	Sulfonamides, penicillin	Unaffected	Died
6	Cairns et al.	?	?	?	IT = 100,000 units	IT = 100,000 units	Sulfonamides	Rapid deterioration	Died in 7½ days
7	Merwarth et al.	23	Meningococcal meningitis	?	IT = 50,000–100,000 units IM = 1 gm.	IT = 500,000 units IM = 14.5 gm.	Sulfadiazine	Rapid improvement	Recovered
8	DeBakey and Pulaski	?	?	?	?	?	?	?	Recovered
9	Stanley	17	Chronic disseminated lupus erythematosus	*B. pyocyaneus* septicemia, with terminal meningitis	SC = 250,000 units–500,000 units	SC = 5,810,000 units	---------	Transitory improvement	Died

IT = intrathecal; IV = intraventricular; IM = intramuscular; SC = subcutaneous

sulfadiazine for four days without any beneficial effect before therapy with streptomycin was started; the antibiotic agent produced rapid improvement and complete recovery. The second case described by these authors (Case 2) was 11 days of age and received four days of ineffective penicillin therapy (intramuscular and intrathecal) before streptomycin was started three days later. The use of this drug led to gradual improvement but there was evidence of residual central nervous system damage. The neurological sequelae may have been due to the greater virulence of the organism and the delay in treatment. Case 3 was not reported in detail but the strain of *Ps. pyocyanea* recovered from the spinal fluid became totally resistant to streptomycin during treatment and the patient died. Three patients, all of whom died, were reported by Cairns and his co-workers (Cases 4, 5, 6). The first two individuals were first treated with streptomycin, penicillin, and sulfadiazine 10 days after the onset of their disease, by which time each had apparently developed a block at some point in the cerebrospinal pathway. The third case was not reported in detail; the subject is said to have been severely ill but not moribund at the time of his first injection but died 7½ hours after treatment was begun.

The patient reported by Merwarth, et al. (Case 7) was a young woman who developed *Ps. pyocyanea* meningitis following intrathecal administration of penicillin for meningococcal meningitis. Improvement was dramatic after the exhibition of streptomycin, but three weeks after discontinuation of treatment, a lower motor neuron lesion affecting all four extremities developed; this regressed partially during the next eight months. The neurological sequela was attributed by the authors to a neuro-toxic reaction caused by the streptomycin. A case of pyocyanea meningitis (Case 8) successfully treated with streptomycin was described by DeBakey and Pulaski; no details were given. The patient reported by Stanley (Case 9) developed *Ps. pyocyanea* bacteremia during the last stages of disseminated lupus erythematosus. Subcutaneous administration of streptomycin was begun shortly after the diagnosis was established and continued until death about 60 hours later. Meningitis was discovered at necropsy and was presumed to be due to *Ps. pyocyanea* although the meningeal exudate was not cultured. No intrathecal streptomycin was given.

It is the purpose of this report to present three cases of meningitis due to *Ps. pyocyanea* occurring after administration of a spinal anesthetic. All of the patients were treated with streptomycin and sulfonamide and recovered.

Case 1. The patient, a 16 year old white male high school student, was referred to the John C. Haynes Memorial Hospital from another hospital because of meningitis. Nine days before admission here he underwent an appendectomy for recurrent bouts of lower abdominal pain. Anesthesia was produced by the intraspinal injection of pontocaine-glucose solution. Two days postoperatively a severe headache and a rise in temperature developed. Penicillin was administered intramuscularly but fever and headache persisted, the neck became stiff, and a positive Kernig's sign became apparent. Three days before admission lumbar puncture revealed the cerebrospinal

fluid to contain 800 cells (type not determined). Cultures of the fluid grew out *Ps. pyocyanea*. Because of this finding, 0.25 gram of streptomycin was given intramuscularly every three hours for 24 hours. On the day before admission the spinal fluid was found to be cloudy and to contain 2425 cells, of which 90 per cent were polymorphonuclear leukocytes and 10 per cent lymphocytes. The sugar and protein content were within normal limits; a rare gram negative rod was found on gram stained smears. At the time of this lumbar puncture 0.1 gram of streptomycin was injected intrathecally, and the intramuscular dose was increased to 0.5 gram every three hours. Culture of the fluid again yielded *Ps. pyocyanea*. This strain was found to be sensitive to 7.8 units of streptomycin per c.c.

On admission to the Haynes Memorial Hospital the patient appeared mildly ill and complained only of headache. The temperature was 101° F., the pulse 78, the respirations 24, and the blood pressure 122 mm. Hg systolic and 70 mm. diastolic. Physical examination was negative except for moderate stiffness of the neck and weakly positive Kernig's sign bilaterally. Lumbar puncture revealed an initial pressure of 250 mm. of spinal fluid, 396 cells, of which 83 per cent were neutrophiles and the remainder lymphocytes. An occasional gram negative rod was seen on smear, but no organisms were obtained on culture. Total protein was 83 mg. and sugar 70 mg. per 100 c.c. The peripheral white blood count was 13,900, with 78 per cent polymorphonuclear leukocytes, 18 per cent lymphocytes, and 4 per cent monocytes. The urine was not remarkable.

The patient was continued on the intramuscular schedule of streptomycin begun before transfer and given 0.1 mg. of the drug intrathecally every 24 hours, in addition. He continued to maintain an irregular elevation of temperature which never exceeded 102.6° rectally, however. Headache disappeared overnight, and the stiffness of the neck became less marked. By the fourth hospital day the cerebrospinal fluid cell count, which had fallen each day, had decreased to a total of 45 per cu. mm., of which 90 per cent were lymphocytes; no organisms had been seen in gram stained smears or recovered on culture. On the fourth hospital day the intramuscular streptomycin was discontinued and three days later the intrathecal use of the drug was halted; at this time the spinal fluid contained 180 cells, of which 90 per cent were lymphocytes; cultures of the spinal fluid remained negative.

Coincident with the cessation of intraspinal streptomycin therapy, the temperature, which had been slightly elevated, fell to essentially normal levels and remained so for three days. During this period the patient felt well, had a supple neck, the Kernig's signs were negative, and he was allowed up in a chair. On the fourth day after treatment was stopped, the temperature rose to 101° and a mild headache was present. The neck remained supple, and the Kernig's signs were negative. Lumbar puncture yielded a cloudy fluid containing 1340 white blood cells, of which 84 per cent were neutrophiles. No organisms were seen on smear or recovered on culture. Because of these findings, the patient was started on a regimen of 0.1 gram of streptomycin intrathecally and 4 grams of the same drug intramuscularly every 24 hours. In addition he was given an initial dose of 4 grams of sulfadiazine, followed by 1 gram every four hours thereafter.

The headache disappeared within 24 hours and the temperature rapidly returned to normal levels. The cell count of the spinal fluid decreased so that after eight days of therapy only 20 lymphocytes per cu. mm. were present. After about four days of treatment, occasional episodes of vomiting, with little or no nausea, began to occur. Intramuscular streptomycin was stopped after six days but the intrathecal administration of the drug was continued. Three days later, because of persistent vomiting, sulfadiazine was discontinued, and sulfamerazine, 1 gram every 8 hours intravenously, substituted. The neck was still slightly stiff, and the Kernig's weakly positive. Streptomycin treatment was discontinued after the intraspinal injection on this day.

Vomiting ceased the next day and it was possible to give the sulfamerazine by mouth. Thirteen days after reinstitution of therapy, five days without streptomycin, the patient was asymptomatic and lumbar puncture revealed a clear spinal fluid containing only three lymphocytes per cu. mm. Moderate stiffness of the neck and weakly positive Kernig's sign persisted, however. After 12 days of normal temperature while on sulfamerazine therapy alone, the patient had a rise in temperature to 101° but felt entirely well. The sulfonamide was stopped at this time.

After three days without any treatment, a lumbar puncture was performed because of persistent low grade fever, and yielded a slightly cloudy fluid containing 2220 cells per cu. mm., of which 86 per cent were neutrophiles; no organisms were seen on smear or recovered on culture. The patient had no complaints at this time and the only positive physical findings were slight stiffness of the neck and slightly positive Kernig's signs. Intrathecal and intramuscular streptomycin (0.1 and 4 grams respectively per 24 hours) and sulfamerazine orally (6 grams per day) were exhibited again on this day. There was again a rapid progressive decrease in spinal fluid cell count; seven days after treatment was instituted there were only 20 cells, 90 per cent lymphocytes, per cu. mm. The temperature gradually declined to normal levels but rose again on the seventh day of treatment to 101.8°. At this time pain, tenderness, redness, heat, and induration were noted at the sites of injection of streptomycin in both buttocks. Because the elevation of temperature was thought to be due to these local infections and the spinal fluid was essentially normal, intramuscular streptomycin was discontinued on the ninth day of therapy. The temperature returned to normal within 48 hours. Despite laboratory evidence of improvement, the patient's neck and back were stiff, and the Kernig's signs remained positive. Intrathecal administration of streptomycin was stopped after 15 days but sulfamerazine was continued for seven days longer. The spasm of the neck and back muscles gradually decreased.

Two days after all medication had been discontinued, the temperature rose to 101.2°, and pain and stiffness of the neck were present; the Kernig's sign was positive. Neurological examination was otherwise normal and there was no tenderness to heavy percussion over the spine. Lumbar puncture revealed a xanthochromic spinal fluid containing many red blood cells and 5800 white cells, of which 95 per cent were neutrophiles. No organisms were seen on gram stained smears or obtained on culture. Cerebrospinal fluid obtained a few hours later, however, yielded *Ps. pyocyanea.*

Since all the treatment given previously had failed, a trial of large doses of intrathecal penicillin (50,000 units every 12 hours) was decided upon. After four days, when it had been found that the organisms were resistant to 500 units of penicillin per c.c., this drug was stopped. Sulfamerazine therapy was again initiated at this time and continued for four days, following which sulfadiazine was substituted for it and the dose increased so that the patient received 14.5 grams the first day and 12 grams a day thereafter. Studies of the sulfadiazine resistance of the strain of *Ps. pyocyanea* which had been isolated showed that it was inhibited by 25 but not by 5 mg. per 100 c.c. of this drug. Since only 4–5 mg. of sulfonamide per 100 c.c. of spinal fluid had been present on the dosage of sulfadiazine previously employed, about ⅓ of the blood level, it was thought necessary to administer large amounts of the sulfonamide in order to produce an effective spinal fluid level. There was clinical improvement on this regimen and the spinal fluid cell count fell to 104 per cu. mm. in three days. However, six days after the initiation of massive sulfadiazine therapy the temperature rose to 102.2° and there was again pain in the neck. A lumbar puncture revealed 5000 white blood cells, and *Ps. pyocyanea* was still present. Since the organism isolated at the beginning of the present relapse was found to be sensitive to a concentration of 15 units of streptomycin per c.c., this drug was administered intrathecally, 0.1 gram every 24 hours, in addition to the sulfadiazine.

The temperature returned gradually to normal, and the pain in the neck dis-

appeared. The number of cells in the spinal fluid also began to decline. After seven days of intrathecal streptomycin therapy, the intramuscular injection of this drug, 4 grams per day, was added. At about this time the back and neck began to grow very stiff, and hot wet packs were applied, with amelioration of symptoms. All chemotherapy was stopped after the patient had received sulfadiazine for four weeks, intrathecal streptomycin for three weeks, and intramuscular streptomycin for two weeks.

The patient was gotten out of bed and seemed to be feeling well. He remained afebrile but eight days after cessation of treatment vomited several times and complained of slight pain and stiffness in the back of the neck. Although the temperature at this time was normal, a lumbar puncture yielded xanthochromic, bloody spinal fluid which contained 5350 white blood cells per cu. mm. No bacteria could be demonstrated. Intrathecal and intramuscular streptomycin, as well as sulfadiazine, was again administered in the same dosage as in the preceding relapse. Intermittent vomiting and an almost constant complaint of frontal and occipital headache and pain and stiffness of the neck were present. Intravenous hydration and the administration of sulfonamide by vein were necessary frequently. The nuchal discomfort was considerably benefited by hot packs. In order to reduce the frequency of parenteral medication, sulfadiazine was replaced by sulfamerazine, the dose of the latter being 2 grams every eight hours. Vomiting subsided gradually and the other symptoms gradually abated; within a week the spinal fluid cleared remarkably and contained 0 to 10 cells per cu. mm. After four weeks of treatment with streptomycin (intrathecal and intramuscular) and sulfonamides, all medication was stopped.

During the last course of chemotherapy, the patient's hearing, which had been normal for conversational tones, began to fail and he became quite deaf, though never totally so. The deafness seemed to increase somewhat for several days after streptomycin was discontinued and then gradually improved, but was still present in moderate degree at the time of dismissal from the hospital. The stiffness of the neck varied somewhat, and was marked at the time of discontinuance of chemotherapy but began to improve very rapidly after a few days.

Twenty-seven days after cessation of treatment the patient was discharged from the hospital. He had remained afebrile during this time and his neck had become almost normally supple, but slight stiffness of the back still persisted. He had been up in a wheel chair for some time and was able to walk short distances without support. A follow-up visit a month after leaving the hospital revealed complete recovery without any sequelae except for bilateral partial deafness.

The patient received a total of 8.1 grams of streptomycin intrathecally, and 227 grams intramuscularly during the entire course of treatment.

Case 2. The patient was a 58 year old white female who was admitted to the John C. Haynes Memorial Hospital with a diagnosis of meningitis. Four days before admission she had undergone an operation at another hospital for repair of a cystocele and rectocele, anesthesia being produced by the intrathecal injection of procaine solution. On the first postoperative day there was a headache and a rise in temperature. The fever increased, cephalalgia became progressively more severe, and stiffness of the neck became apparent. Three days after operation a lumbar puncture yielded a fluid containing about 4000 cells, all of which were said to be neutrophiles and the patient was sent to the Haynes Memorial the next day. The past history was of significance only in that diabetes had been present for about five years; this was controlled by 16 units of protamine zinc insulin daily and a rather casually followed diet.

The only remarkable findings on physical examination at the time of admission were marked stiffness of the neck, bilaterally positive Kernig's sign, and the evidence of the recent operation, which appeared to be healing normally. Lumbar puncture revealed a pressure of 210 mm. and cloudy spinal fluid containing 3860 cells of which

72 per cent were neutrophiles and 28 per cent lymphocytes; the total protein was 104 mg. and the sugar 34 mg. per 100 c.c. Gram negative rods were seen on smear, and *Ps. pyocyanea* was recovered on culture; the strain was found to be sensitive to 31.5 units of streptomycin per c.c. The urine was free of sugar and ketones and was otherwise not remarkable.

On the day of admission, the patient was placed on a regimen of 0.1 gram of streptomycin intrathecally every 24 hours as well as 0.5 gram of this drug intramuscularly every three hours. For the first three days there was some improvement, with decrease in headache and fall in temperature; on this day the number of cells in the spinal fluid was 810 per cu. mm., of which 82 per cent were neutrophiles and the remainder lymphocytes. No organisms had been demonstrated in smears or cultures of the spinal fluid since the beginning of treatment. On the next day, however, headache was worse, the temperature rose, and the patient felt very ill again. Lumbar puncture revealed 3000 white blood cells, and gram negative bacilli. Because of these findings the intrathecal injections of streptomycin were increased to twice daily (0.1

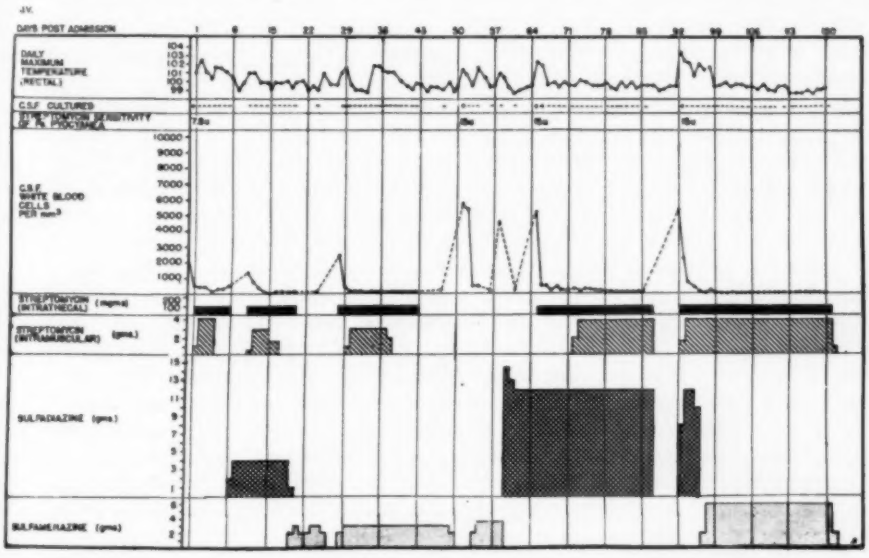

CHART 1.

gram every 12 hours) and sulfadiazine (initial dose of 4 grams, followed by 1 gram every four hours orally) was given in addition. The intramuscular administration of streptomycin was continued as before. The general clinical condition improved rapidly; the headache disappeared and the temperature fell to a normal level in 36 hours. Stiffness of the neck had entirely disappeared seven days after admission. On the evening of the seventh day the patient developed a marked vertical nystagmus and complained of a sensation of "going over a waterfall." Intramuscular streptomycin was discontinued because of these findings and the nystagmus and vertigo disappeared overnight. There was no tinnitus or deafness.

The intrathecal injection of streptomycin was discontinued after 12 days. At this time the spinal fluid contained only 180 cells per cu. mm., of which the great majority were lymphocytes; total protein was 131.6 mg. per 100 c.c., the chloride level was 121.5 m. eq., and the sugar content was normal.

Sulfadiazine was continued through the eighteenth hospital day, the patient remaining symptomatically well and afebrile. On the eighteenth day, there were only

46 white blood cells per cu. mm. of spinal fluid; 91 per cent were lymphocytes. The spinal fluid total protein was decreased to 80 mg. per 100 c.c. and no organisms were seen on smear or recovered on culture.

The patient was allowed out of bed and seemed to be convalescing uneventfully, when on the twenty-third day she had a sudden onset of pain and swelling of the left leg, with tenderness over the calf. A diagnosis of left femoral-iliac phlebothrombosis was made, and at operation a clot was evacuated from the left femoral and iliac veins. The veins of the left leg were ligated but those on the right were not closed because the patient went into shock during operation. Heparin was given for 48 hours post-operatively and then dicoumarol for the next 29 days, the prothrombin time being maintained at an adequate level. The swelling and pain in the affected leg subsided gradually and there was no evidence of further phlebothrombosis or pulmonary infarction.

By the thirty-ninth day the patient was up again in a chair and was free from any difficulty except swelling of the left lower extremity. Shortly after this time she began to complain bitterly of shooting, cramping pain in the lumbo-sacral region which required opiates for relief. No explanation for the pain could be found on physical or roentgenologic examination. Because of the possibility of diabetic neuritis, large doses of the vitamin B complex were given parenterally but the pain persisted and was aggravated by motion to such a degree that there was great reluctance to walk.

Thirty-two days after the discontinuance of all therapy, the temperature suddenly rose to 102° (R). The patient had no complaints other than the persistent pain in the lumbo-sacral region, but the neck was slightly stiff. The spinal fluid contained 6000 white cells per cu. mm., with 80 per cent neutrophiles and 20 per cent lymphocytes, and *Ps. pyocyanea* was obtained on culture. Sulfadiazine, five grams initially followed by 1 gram every four hours, was administered. The temperature returned to normal within 48 hours and the stiffness of the neck disappeared. When the spinal fluid was examined on the third day after the recurrence, it revealed 204 white blood cells, of which 99 per cent were lymphocytes. *Ps. pyocyanea* was recovered in cultures and the strain proved to be sensitive to 30 units of streptomycin per c.c. and to more than 5 but less than 25 mg. of sulfadiazine per 100 c.c. Intrathecal streptomycin injections, 100 mg. every 24 hours, were resumed one week after the recurrence of the meningitis; at this time the spinal fluid contained only 18 lymphocytes per cu. mm. but the Gram negative bacteria were still present. Within the next 24 hours, the temperature, which had been normal, rose to 101.8° (R), with no appreciable change in physical findings; the spinal fluid contained 13,830 white cells per cu. mm. (52 per cent lymphocytes and 38 per cent neutrophiles) and *Ps. pyocyanea*. The fever abated during the next day and there was a rapid fall in the number of cells in the spinal fluid. No organisms were present in this or any of the subsequent spinal fluid cultures. Intramuscular streptomycin (4 grams per day) was added to the other therapy on the fourteenth day of the recurrence of meningitis. At this time vomiting appeared and persisted for several days and the patient began to complain of difficulty in hearing conversational tones.

Twenty-three days after resumption of intrathecal treatment, a series of generalized convulsions, lasting about an hour occurred, and was followed by stupor. A lumbar puncture revealed 550 red cells and 550 white blood cells per cu. mm. (91 per cent lymphocytes). There were no localizing neurological signs or paralysis. Within 24 hours consciousness returned but the patient was euphoric and had some difficulty in recognizing people. Intrathecal streptomycin was discontinued immediately after the convulsive episode and the intramuscular drug as well as sulfadiazine was omitted five days later. Severe cramping pains in the buttocks appeared at about this time and persisted until discharge. An epidural injection of procaine

(1 per cent) at the junction of the sacrum and coccyx, followed by the instillation of 100 c.c. of saline, produced only transitory relief of the discomfort. The deafness, which was more severe in the right than the left ear, also persisted and, although moderately severe, was not complete.

The patient gradually became ambulatory, remained afebrile, and was free of any sign of meningeal irritation. The lumbar, sacral, and buttock pain waxed and waned in severity but frequently could be relieved by 0.3 gram of acetylsalicylic and/or by placebos. The euphoria noted immediately after the episode of convulsions gave way to alternating periods of depression and elation.

In this condition the patient was discharged from the hospital 111 days after admission. Follow-up reports during the next six weeks revealed persistence of the pain in the back with resultant difficulty in walking. An arachnoiditis was presumed to be the cause of the severe lumbo-sacral discomfort. During the entire course of treatment, a total of 2.9 grams of streptomycin had been administered intrathecally and 83 grams given intramuscularly.

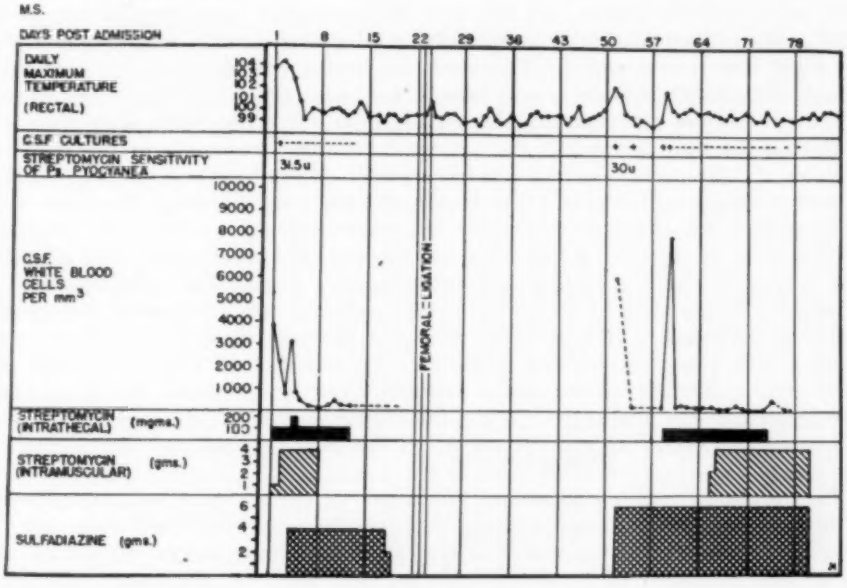

CHART 2.

Case 3. The patient was a 33 year old white married woman who was subjected to appendectomy under a spinal anesthesia with pontocaine-glucose solution. She remained in the hospital for 12 days after operation, and was quite well except for occasional pain in the flanks and a mild headache. Soon after returning home, she began to have generalized malaise, a constant throbbing headache, stiffness of the neck, and fever ranging from 101°–102° F. The headache grew steadily worse and vertigo, tinnitus, and paresthesias of both arms developed.

Nineteen days after operation, the patient was admitted to the Haynes Memorial Hospital with a diagnosis of meningitis. Physical examination on admission revealed stiffness of the neck and back, a healing right lower quadrant scar, negative Kernig's signs, and brisk, equal deep tendon reflexes. There was slight papilledema and moderate engorgement of the retinal veins bilaterally. The temperature was 100.6° F. The cerebrospinal fluid was under a pressure of 250 mm. and contained 1656 white

blood cells per cu. mm. (66 per cent neutrophiles and 34 per cent lymphocytes); the sugar was 61 mg. and the total protein was 75.2 mg. per 100 c.c. An occasional gram negative rod was seen on examination of spun sediment, and *Ps. pyocyanea* was obtained on culture. The peripheral white blood count was 10,600, with 95 per cent neutrophiles and 5 per cent lymphocytes. The strain of *Pseudomonas* was sensitive to 15 units of streptomycin per c.c.

Streptomycin, 0.1 gram intrathecally and 4 grams intramuscularly, as well as 6 grams of sulfadiazine, was administered every 24 hours as soon as the diagnosis was established. The headache improved rapidly and disappeared within 24 hours. Because of difficulty in voiding urine, a Foley catheter was inserted and left in place. Urinary output was adequate until the morning of the fourth hospital day when for a period of 14 hours only about 10 c.c. of extremely bloody fluid was passed through the catheter. Administration of sulfonamide and intramuscular streptomycin was stopped within two hours of the time of cessation of urine output, after it had been established that the catheter was patent, and a moderate amount of fluid was given intravenously. After 14 hours the urine flow was reëstablished and 3750 c.c. were voided in the next 12 hours. At this time, intramuscular streptomycin therapy was started again and six days later sulfamerazine (2 grams initially followed by 1 gram every eight hours) was added. There was no further episode of anuria or oliguria, although microscopic hematuria was present for about six days. The Foley catheter was removed on the ninth hospital day, and normal micturition took place thereafter.

During the next few weeks the patient complained frequently of prickling sensations on the face, and over the extremities and, on one occasion, showed extensor spasm of the legs and left arm. She developed back pain, centering about the site of the injections; this disappeared rapidly after a reassuring conversation. Pain and paresthesias in the legs and thighs occurred sporadically. Five weeks after admission to the hospital the knee and ankle jerks on both sides disappeared completely and had not returned at the time of discharge. Pain and light touch sensation and position sense remained intact. Tinnitus began to appear and progressed until it was constant. Deafness, which was first noted about the eleventh day of treatment, progressed rapidly until it became almost total. Intramuscular streptomycin was discontinued on the thirteenth day, and some increase in hearing became apparent within 48 hours, but improvement thereafter was very slow. Stiffness of the back and neck disappeared quite slowly.

Ps. pyocyanea was not recovered in cultures of the cerebrospinal fluid after the first lumbar puncture, although attempts to grow the organisms were made daily for 18 days. The number of white cells in the spinal fluid decreased to 192 per cu. mm., with a preponderance of lymphocytes, after one week of treatment. Intrathecal streptomycin was discontinued on the eighteenth hospital day.

The patient was allowed to sit in a chair in the sixth week and soon thereafter attempts were made to induce her to walk. It was apparent that marked incoördination of muscles of the lower extremities was present. The Romberg test was positive, but not lateralized. Caloric stimulation of the vestibular apparatus was attempted on three occasions, without production of nystagmus, past pointing, vertigo, or falling to either side. No other sensory impairment occurred during the course of the illness. Massage and active and passive exercises were carried out and gradually the patient learned to walk without help but only with her eyes open.

Sulfamerazine was discontinued on the twenty-seventh hospital day. One week later the cerebrospinal fluid contained only 26 cells per cu. mm., of which 92 per cent were lymphocytes; the total protein remained elevated to 186 mg. per 100 c.c.

The patient ran a low grade, irregular fever (100°–101.2° F.) constantly for the first 13 days of her hospital stay. After discontinuing intramuscular streptomycin, the temperature returned to normal and remained so during the rest of the hospital

stay. During the six weeks following cessation of all chemotherapy (the entire course is not depicted in chart 3), stiffness of the neck and back entirely disappeared. Hearing improved gradually, so that at the end of the period the patient could understand loud conversation. Tinnitus, described as "bells" or "crackling of paper" superimposed on a low pitched "droning," continued sporadically, but seemed progressively less severe.

A total of 1.8 grams of streptomycin was administered intrathecally and 36.5 grams given intramuscularly during the course of treatment. A follow-up examination six weeks after discharge from the hospital revealed the patient to be quite well. She still complained of tinnitus and deafness was moderate, but she was able to walk well except in the dark.

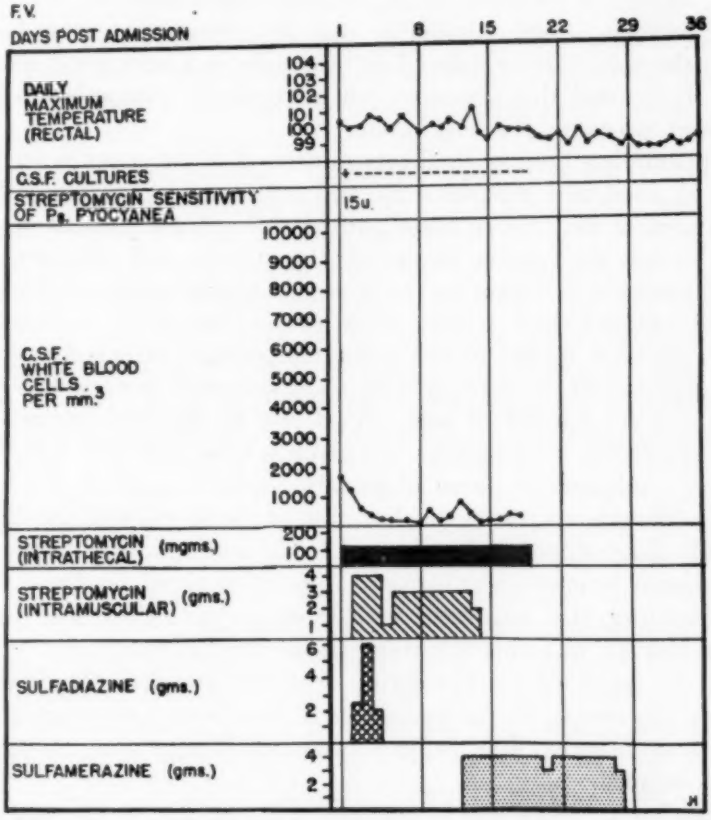

CHART 3.

DISCUSSION

In the light of the previously recorded observations that the majority of primary meningitides due to *Ps. pyocyanea* results from the introduction of the organisms during the course of spinal or cisternal punctures for diagnostic or therapeutic purposes, it is important to emphasize the fact that all three of the cases reported in this paper followed the instillation of a spinal

anesthetic; in two instances pontocaine-glucose solution was used and in the third, procaine was injected. All of the cases occurred in the same hospital during a 13 day period and were treated by the same anesthetist; no other cases of this type were seen in this hospital subsequently. No information could be obtained concerning the source of the organisms which were found in the spinal fluid, since none of the solutions used were available for bacteriologic examination; it must be presumed, however, that they were introduced at the time of production of spinal anesthesia. Careful check of the sterilization procedures revealed no errors which might have allowed contamination of the instruments used during the production of the spinal anesthesia. Cultures of the skins of the affected individuals did not reveal the causative bacteria. The possibility that *Ps. pyocyanea* may have been present in the materials introduced intrathecally is a very good one since it has been shown that this organism not infrequently contaminates solutions of boric acid, procaine, fluorescein, etc.[1]

An outstanding finding in the treatment of these cases was the rapid response to combined streptomycin and sulfonamide therapy. The protracted course of the first of these patients offered an unusual opportunity to assess crudely the relative merits of streptomycin and sulfonamide, alone and in combination. Whenever streptomycin was administered by the intrathecal and intramuscular routes, alone or together with sulfonamide, the patient's symptoms tended to abate, the temperature returned towards normal, the spinal fluid, if infected with *Ps. pyocyanea,* became sterile within 48 hours, and the number of white blood cells in the fluid declined towards normal. Penicillin intrathecally was given a brief trial but was singularly ineffective. Sulfonamide, used alone, also failed to control the meningeal infection, although temporary amelioration of the severity of the disease was produced by large doses of this drug; 12 grams of sulfadiazine per day produced moderate improvement for only a period of about six days. It would appear, therefore, that treatment with streptomycin is the sine qua non of successful therapy of primary meningitis due to *Ps. pyocyanea.* That caution must be exercised in considering a patient cured of the disease is indicated by the course of events in case 2, in whom a recurrence, with repeatedly positive spinal fluid cultures occurred 32 days after all therapy had been discontinued.

Although *Ps. pyocyanea* is considered to be one of the organisms in which resistance to streptomycin develops with great ease [6, 9] it is noteworthy that in none of the cases reported here did the causative bacteria show any tendency to become resistant. In both patients in whom relapses occurred, the strains isolated at various times during the course of the disease showed no essential change in sensitivity to streptomycin. In case 1, during four recurrences, the organism was sensitive to 7.8 to 15 units of the drug per c.c., while in case 2, the bacteria isolated 32 days after cessation of treatment were no more resistant than they were before being exposed to the antibiotic agent.

The important complications which occurred during the course of treatment were the result of involvement of the eighth cranial nerve. All of the patients developed a marked degree of deafness during therapy. In case 3, loss of hearing appeared in the first week in the hospital, shortly after the inception of streptomycin administration. This patient had tinnitus prior to admission but this subsided during the first few days of hospitalization and she did not complain of it again until after the onset of deafness. In the other two cases clinically apparent deafness developed only after reinstitution of streptomycin treatment because of a relapse of the disease. There was improvement in hearing of all of the patients following discontinuation of antibiotic therapy. Because of the hopeless outlook of the disease without streptomycin treatment, all patients continued to receive the drug after impairment of hearing became obvious. The specific rôles played by the meningitis and the streptomycin in the production of the deafness cannot be evaluated with certainty.

Disturbance of the vestibular apparatus appeared in two of the patients (cases 2 and 3). In case 2, the disturbance was transitory, consisting only of the brief episode of vertigo, accompanied by a gross vertical nystagmus. In case 3 complete bilateral loss of vestibular function occurred without any associated neurological dysfunction except deafness. Despite this impairment the patient learned to walk again and had no difficulty as long as she was able to orient herself in space visually. So good was her compensation, in fact, that when last seen, 97 days after her discharge from the hospital she was resuming her former hobby of fencing.

The transitory episode of anuria which occurred in case 3 is of considerable interest, although no conclusions can be drawn as to its etiology. The patient was receiving both streptomycin and sulfadiazine at the time, but sulfonamide crystalluria was absent and the urine was alkaline at the time of the incident. Streptomycin therapy was reinstituted as soon as urine formation was observed, and sulfamerazine was given subsequently without any further difficulty except for slight albuminuria for nine days after the incident of anuria. The block to urine flow was probably not due to sulfonamide lithiasis with blockage, but it is possible that an acute lower nephron nephrosis, which has been observed with the sulfonamides, occurred. The rapidity with which all of the manifestations cleared and the absence of further difficulty on resumption of sulfonamide administration militates somewhat against a drug nephrosis. Whether or not streptomycin could have been responsible for the sudden anuria cannot be stated. Some evidence has been presented in the literature indicating that this antibiotic agent may cause decrease in urine formation. Streptomycin injection was associated with a decrease in urinary output in two individuals studied by Rutstein et al.,[10] and depression of water diuresis by the same lot of drug was noted by Molitor and co-workers in rats [11]; the material used was a concentrate which was thought to be relatively impure. Madigan et al.[12] also

noted an antidiuretic effect in rats. Hyalin and granular casts have been found in patients receiving crystalline streptomycin.[13] Transient fatty infiltration of the kidneys has been found in monkeys, following administration of streptomycin parenterally.[11] So far as can be determined, however, no case of anuria in man attributable to streptomycin has been reported.

It is interesting to point out that the recurrences of meningitis in cases 1 and 2 were accompanied by the presence of a variable number of red blood cells and occasionally by xanthochromia in the spinal fluid. While the possibility of traumatic lumbar punctures cannot be ruled out, it seems very likely that a true hemorrhagic meningitis was present at these times. *Ps. pyocyanea* is known to produce a hemorrhagic meningitis in swine,[14] and the organisms show a strong tendency to localize in the smaller blood vessels with the production of thrombosis. This, together with the proteolytic action of these bacteria on tissues, may be responsible for bleeding.

Conclusions

1. Three cases of primary meningitis due to *Ps. pyocyanea* successfully treated with intrathecal and intramuscular streptomycin and sulfadiazine or sulfamerazine have been described.

2. All of the cases resulted from infection of the meninges during the course of production of spinal anesthesia. The source of the organisms could not be determined.

3. Two patients showed from one to four relapses of the meningeal infection when treatment was stopped.

4. Deafness occurred as a complication in all of the patients and one individual showed severe labyrinthine disturbance with complete loss of vestibular function.

5. Hemorrhagic meningitis may be produced in man by *Ps. pyocyanea.*

6. The strains of *Ps. pyocyanea* responsible for the infections described in this paper were sensitive to between 7.8 and 30 units of streptomycin per c.c. and did not become resistant to the drug during treatment.

7. Streptomycin, in combination with sulfadiazine or sulfamerazine, appears to be the therapy of choice in primary *Ps. pyocyanea* meningitis.

BIBLIOGRAPHY

1. Stanley, M. M.: *Bacillus pyocyaneus* infections. A review, report of cases and discussion of newer therapy including streptomycin, Am. Jr. Med., 1947, ii, 253–277, 347–367.

2. Harris, R. C., Buxbaum, L., and Appelbaum, E.: Secondary *Bacillus pyocyaneus* infection in meningitis following intrathecal penicillin therapy, Jr. Lab. and Clin. Med., 1946, xxxi, 1113–1120.

3. Cairns, M., Duthie, E. S., and Smith, H. V.: Intrathecal streptomycin in meningitis. Clinical trial in tuberculous, coliform and other infections, Lancet, 1946, ii, 153–155.

4. Merwarth, H. R., Rosenberg, H., and Pulito, F.: Pyocyaneus meningitis followed by unusual complications attributed to treatment with streptomycin, Brooklyn Hosp. Jr., 1947, v, 93–96.

5. PAINE, T. F., MURRAY, R., HARRIS, H. W., and FINLAND, M.: Streptomycin in the treatment of certain gram-negative bacillus infections of the central nervous system, Am. Jr. Med. Sci., 1947, ccxiii, 676–685.
6. PAINE, T. B., and FINLAND, M.: The use of streptomycin in the treatment of meningitis, Med. Clin. North Am., Boston Number, 1947, 1092–1105.
7. DEBAKEY, M. E., and PULASKI, E. J.: An analysis of the experience with streptomycin in United States Army hospitals. Preliminary report, Surgery, 1946, xx, 749–760.
8. MURRAY, R., PAINE, T. F., and FINLAND, M.: Streptomycin. I. Bacteriological and pharmacological aspects, New England Jr. Med., 1947, ccxxxvi, 701–712.
PAINE, T. F., MURRAY, R., and FINLAND, M.: Streptomycin. II. Clinical uses, *Ibid.*, 1947, ccxxxvi, 748–760.
9. MURRAY, R., KILHAM, L., WILCOX, C., and FINLAND, M.: Development of streptomycin resistance of gram negative bacilli in vitro and during treatment, Proc. Soc. Exper. Biol. and Med., 1946, lxiii, 470–474.
10. RUTSTEIN, D., STEBBINS, R., CATHCART, R., and HARVEY, R.: The absorption and excretion of streptomycin in human chronic typhoid carriers, Jr. Clin. Invest., 1945, xxiv, 898–909.
11. MOLITOR, H., GRAESSLE, O., KUNA, S., MUSHETT, C., and SILBER, R.: Some toxicological and pharmacological properties of streptomycin, Jr. Pharmacol. and Exper. Therap., 1946, lxxxvi, 151–173.
12. MADIGAN, D. G., SWIFT, P. N., and BROWNLEE, G.: Clinical and pharmacologic aspects of toxicity of streptomycin, Lancet, 1947, i, 9–11.
13. Committee on Chemotherapeutics and Other Agents. National Research Council. Streptomycin in treatment of infections: Report of one thousand cases, Jr. Am. Med. Assoc., 1946, cxxxii, 4–11, 70–76.
14. KOSKE, F.: Der *Bacillus pyocyaneus* als Erreger einer Rhinitis und Meningitis Hemorrhagica bei Schweinen, Arb. a. d. k. Gsndhtamte., Berlin, 1906, xxxiii, 542–553.

THE CHALLENGE OF PREVENTIVE MEDICINE*

By James Stevens Simmons, F.A.C.P., Brig. Gen. U. S. Army, Retired;
Dean, Harvard School of Public Health

Mr. President, Members of the American College of Physicians, Ladies and Gentlemen:

I appreciate deeply the honor of being asked to give the James D. Bruce Memorial Lecture on Preventive Medicine for 1948. It is a pleasure to attend this Convocation and to be here with so many good friends.

I welcome the opportunity to discuss such a timely subject with this distinguished group of leaders in American Medicine, for I am sure there has never been a period in the history of the country when preventive medicine was of such vital importance to our national welfare and security. We are living in a dangerous age and no one knows where the world is heading; whether toward a firm peace, a continuation of the present armed truce, or another war. Regardless of the answer, the United States will need all of its potential strength—physical, mental and moral—to enable it to meet successfully whatever the future may bring. As physicians, we now face a challenging opportunity for service which is perhaps the greatest ever afforded to any profession; for we are privileged to use our full leadership in the important task of building a healthier, stronger nation.

With this opportunity in mind, I have chosen as the subject of today's talk: "The Challenge of Preventive Medicine." In order to visualize this challenge, it is suggested that we define preventive medicine, trace its development as a constructive factor in national security, estimate its future potentialities, and then consider how we can increase our contribution in this important field.

Definition

Preventive medicine has the same broad objective as public health; namely, the promotion of individual, community, state and national health. Both specialties are concerned with the prevention of disease and the protection of physical and mental health. As Smillie (1947) has pointed out, however, they may be differentiated on the basis of responsibility. According to him, the term "public health" includes those preventive activities which are recognized as a community responsibility, while the term "preventive medicine" is usually restricted to activities which are the responsibility of the individual. Obviously, these services overlap, but regardless of whether one is dealing with individual preventive medicine, as it is practiced by the family

* The "James D. Bruce Memorial Lecture on Preventive Medicine for the year 1948," delivered at the Convocation of the American College of Physicians, San Francisco, April 19, 1948.

physician, or with community preventive medicine, as carried out by the specialized profession of public health, the final responsibility for leadership still rests on medicine and its allied professions. Therefore, for the purpose of this discussion, it is suggested that we define preventive medicine as the sum total of all those services required to prevent disease and to keep well people well. Acceptance of this definition implies no decreased appreciation of the importance of curative medicine, but rather adoption of the viewpoint that the entire profession, regardless of specialty, has a responsibility for disease prevention and health promotion.

This concept is not new. It has been preached for years, and it is now practiced faithfully by many physicians and surgeons—particularly the pediatricians and obstetricians. In fact, one of our greatest clinicians, Sir William Osler, made the prediction years ago that "preventive medicine is the medicine of the future. The time has come to ask ourselves how completely we are living up to this broad concept of service and how far we have advanced toward Osler's vision of the medicine of the future. The answer can be found by reviewing the progress already made, and by making a brief inventory of some of the major health problems which still exist.

Past Accomplishments

The medical profession of this country can be proud of its past achievements both in curative and preventive medicine. The entire structure of modern medicine has been built within a single century, and much of this progress has occurred during the last 50 years.

The physicians who gathered in Philadelphia on May 7, 1847, to establish the American Medical Association knew nothing about the causes of the infectious diseases with which they worked, and the few pioneer health departments of that day were handicapped by the same universal ignorance. In 1872, when the American Public Health Association was organized by a public-spirited New York physician, Dr. Stephen Smith, the new science of bacteriology was just being born; but health conditions were not much better. The Civil War had been fought without benefit of military preventive medicine and the troops had been ravaged by most of the ancient plagues of war. In that year, the death rates in many American cities exceeded 30 per thousand, the infant mortality ranged from 150 to 200 per thousand live births, and the life expectancy at birth was only about 40 years (Dublin, 1943). Epidemics were common and the United States was frequently invaded by such exotic diseases as Asiatic cholera, European typhus, and yellow fever from the Caribbean.

By the end of the 19th century, information had been discovered about the etiology, diagnosis, transmission and treatment of a number of infectious diseases. Microbiology, immunology, physiology, biochemistry and other medical specialties were developing rapidly. Insects had recently been incriminated as the vectors of certain diseases, including malaria. Medical

research was expanding, and some progress had been made in applying the new discoveries to the prevention of disease. However, the health situation in the United States still left much to be desired. Most of the endemic diseases were still prevalent, and at times they caused serious epidemics. The troops in the Spanish American War were seriously crippled by typhoid and the disease death rates were seven times as high as those caused by battle injuries. In spite of quarantine, the country was still being invaded by exotic diseases. The death rate for the year 1900 was 17.2 per thousand, the infant mortality was more than 100 per thousand, and the life expectancy was only 47 years.

From this time on, the picture became brighter and much progress has been made. Although it is a temptation to trace the course of that progress, it will serve our present purpose merely to show that a measurable improvement has been made and to indicate some of the factors concerned.

A careful study of these factors reëmphasizes the importance of fundamental medical research to the improvement of health. It also shows that unless there is intelligent planning and vigorous application of the knowledge available, considerable time may be required to translate the products of research into action. This lag shows up in the vital records of the first two decades of the present century—a period when there was little popular or professional interest in public health, when trained health workers were scarce, and when the administration of official health services was left largely in the hands of incompetent politicians. Since that time, interest in preventive medicine has been increasing. Under the stimulus of various voluntary health agencies and philanthropic foundations, special schools have been established for the training of public health administrators; governmental health agencies have become more active at community, state and federal levels; and the total health coverage of the nation has been gradually expanded. The greater interest of the people and of the Federal Government during the last two decades is indicated by such significant events as President Hoover's White House conference on child welfare in 1930, and President Roosevelt's program of national security in 1935 which resulted in the Social Security Act. This legislation provided better national health services under the leadership of the United States Public Health Service and, at the same time, it has insured considerable independence of action by the states and their communities. When our country entered World War II, this program was well under way, and American health had reached a relatively high level. At that time the crude death rate for the Registration Area had decreased to a low of about 10.8 per thousand, the infant mortality had dropped to 47 per thousand live births, and the average life expectancy at birth had risen to about 64 years.

The unusual hazards of the war afforded a crucial test of our health resources. The success with which this test was met is known to all of us. The enormous war-time health program was actively supported and operated

by the united professions of medicine and public health, both civilian and military, although it was spearheaded by the programs of the Army and Navy. In the Army alone, more than 10 million men were mobilized to serve in some of the most unhealthful regions of the world; yet the disease rates were lower than in any of our former wars. Military medicine and surgery reached a high degree of efficiency. Many of the diseases which crippled our troops in previous wars, such as smallpox, typhoid, typhus and tetanus, were completely controlled. Other infections, especially malaria and the dysenteries, caused considerable disability in overseas theatres. However, there were no great epidemics, and the disease death rate was only 0.6 per thousand. This is a relatively low figure when compared with the rate of 15.6 for the first world war, and with 25 for the Spanish American war.

In commenting on this record, Winslow, Boudreau and Hume (1947) recently made the following statement: "Our allied armies planned their defenses against disease as carefully and scientifically as they planned for protection against airplanes and submarines; and it is an astounding fact that World War II was the first major conflict in history which was not followed by major epidemic diseases. Public health science has at its disposal today defensive weapons of unparalleled power and effectiveness."

Civilian health also continued to improve. Last year (1947) the death rate for the entire nation reached a new low of 10 per 1,000, and the expectation of life at birth rose to an all-time high of about 66 years.

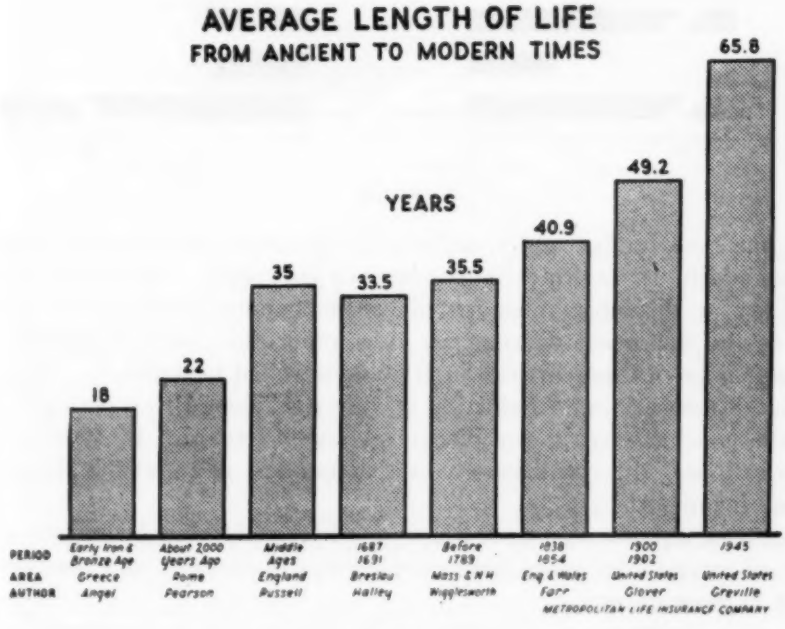

FIG. 1.

Unsolved Problems

This is an excellent record of progress, especially when viewed against the background of the profound medical ignorance of the recent past. However, when one compares the death rates for different diseases in 1900 with the rates in recent years, it is apparent that the improvement has not been general. As shown in figure 2, the most spectacular reduction in mortality has occurred in the diseases that commonly attack children and young adults, but there has been little improvement in the rates for the degenerative conditions which afflict people in the later half of life. The main reason for presenting this graph, however, is to emphasize the fact that many people still die of diseases which are preventable, such as the infections included in the venereal, intestinal and insect-borne groups.

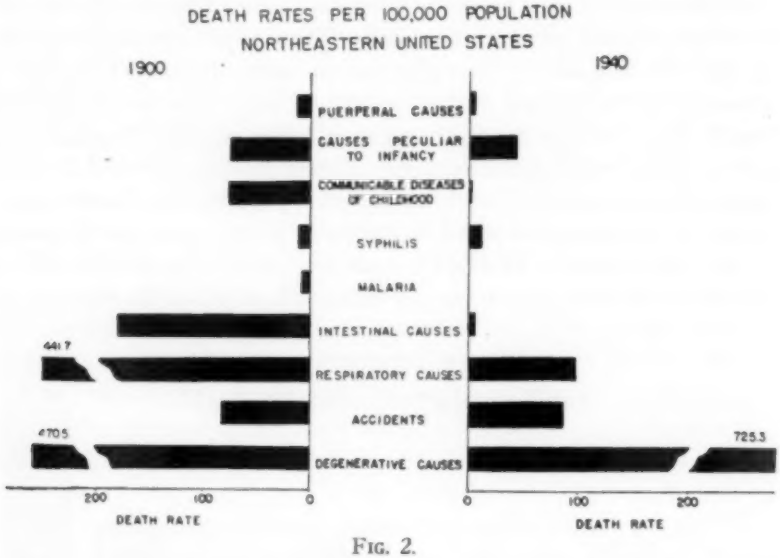

Fig. 2.

If one goes further and considers the sickness and disability caused by disease, additional health problems become apparent. We do not have the morbidity or disability rates for the entire country since 1900; however, most of the important diseases are now reportable, and the prevalence of certain groups of these diseases in 1946 is indicated in figure 3. This graph brings out the fact that a reduction in mortality alone is not enough to warrant the conclusion that any disease is under control. It deserves closer study by those who speak loosely of the conquest of infectious disease as a job that is finished.

One can visualize the unfinished task by considering briefly the present status of some of the more important groups of diseases and conditions included in these graphs.

1. *The Problems of Maternity and Infancy.* It is suggested that we start with the problems of maternity and infancy. Maternal mortality has

been decreased enormously within the last decade by improvements in the practice of obstetrics; and the maternal death rate, which was about 6 in 1937, reached an estimated low of 1.3 last year. The infant mortality has also declined from well over 100 per thousand in 1900 to an estimated 34.0 in 1947—a reduction of about 66 per cent. Earlier, this reduction was gradual, and apparently it resulted from various factors, including: the general improvement in living conditions, better sanitation, safer milk supplies, and better medical practice. During the last decade, the mortality has decreased more rapidly through the development of special pediatric care and child health services. The improvement, however, has not been uniform. In 1944, for example, when the total infant mortality for the United States was about 40.0, some of the states still had rates of 68.0, or more, indicating that serious health problems still exist in this field. The national survey

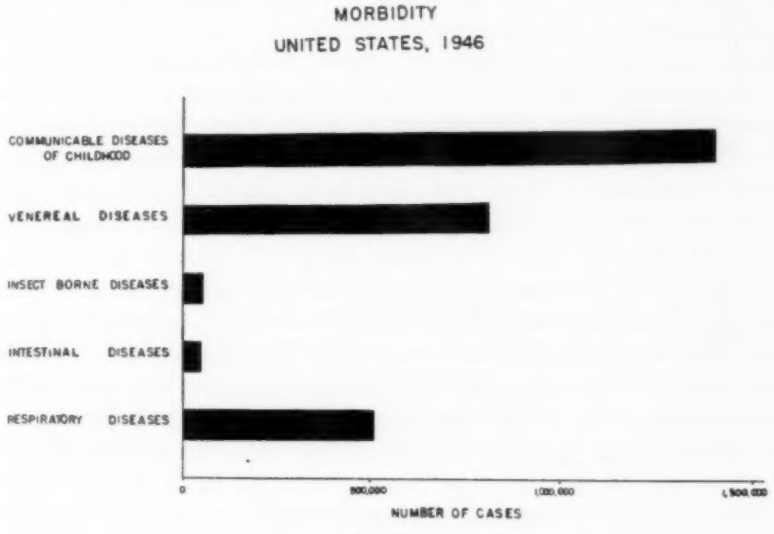

FIG. 3.

of child health services now being made by the Academy of Pediatrics, should help to define these problems and point the way to further improvement.

2. *Diseases of Childhood.* An even more remarkable reduction has occurred in the death rates for the communicable diseases of childhood. Fifty years ago, the combined mortality rate for measles, scarlet fever, whooping cough, diphtheria and meningitis was 75 per 100,000. In 1940, it was only 2.5—a reduction of about 97 per cent. However, this group of infections illustrates the fact that death rates may be reduced without a corresponding decrease in morbidity. In 1946, for example, measles ranked first among all the communicable diseases reported in the United States—with a total of about two-thirds of a million cases. Moreover, five of the ten leading communicable diseases reported that year were childhood infections. Chickenpox caused a quarter of a million cases, mumps 160,000, scarlet fever

118,000, and whooping cough 104,000. Yet none of these infections appeared among the 15 major causes of death in 1945, the latest figures available, although whooping cough is still an important cause of mortality in early life.

The decreased mortality for these diseases cannot be attributed to specific prophylactic measures. It has resulted largely from the use of more effective chemotheraputic agents and to a general improvement in treatment and medical care. The fact that they are still leading causes of sickness, and that they produce much suffering and disability, makes it important to continue the search for methods with which to prevent them.

Epidemic meningitis is less important as a cause of death, since effective methods are available for treatment with the sulfonamides. Army field investigations show that sulfadiazine may be used effectively for the cure of meningitis carriers and for controlling epidemics, but better methods are still needed to prevent this disease.

Diphtheria belongs in a different category, for it is a preventable disease. The death rate has shown a larger decline than any of the other childhood infections. Before 1921, this resulted from the fact that more was known about its diagnosis, epidemiology and control; and antitoxin was available for specific treatment. Since that time both the mortality and morbidity have been decreased enormously by the immunization of large groups of children. Many of these immunization programs were stopped during the war, and diphtheria has increased slightly in the last two years. In 1946, for example, there were more than 16,000 cases and 1,300 deaths. These cases and deaths should not have occurred. The disease can be eradicated if all the states will provide for coördinated immunization programs to be conducted continuously in the schools, using diphtheria toxoid.

Poliomyelitis also presents a different problem, since there is no information as to specific treatment or prevention. In 1946, 25,000 cases were reported in the United States. Better methods for medical care and rehabilitation have been developed and it is hoped that the researches sponsored by the National Foundation for Infantile Paralysis and other agencies may eventually lead to its control.

3. *Respiratory Diseases.* The acute respiratory diseases, including the common cold, influenza, and the pneumonias, also present serious problems in prevention. In the records for 1945 and 1946 pneumonia and influenza were still listed among the 10 leading causes of disease, and also the 10 leading causes of death. However, the death rates are decreasing rapidly and they will be reduced further by the more general use of the sulfonamides and penicillin.

Progress is also being made in the development of immunizing agents. Researches sponsored by the Army Epidemiological Board show that several types of pneumococcus pneumonia can be prevented by immunization with polysaccharide antigens (Blake, 1945). The extensive use among troops of the Army influenza vaccine, developed by Francis and his co-workers of

the Influenza Commission, shows that protection is afforded against certain types of virus, and suggests the possibility of controlling this disease with vaccines containing a wider range of viruses.

The common cold is an important cause of temporary disability and economic loss. It has been estimated that colds cause the people of the United States to suffer discomfort and reduced efficiency for about one and one-half billion days each year. The annual cost has been estimated at more than 420 million dollars in lost wages plus sufficient expense for drugs and medical care to make a total of about one billion dollars. Thus the common cold still remains a major challenge to preventive medicine.

Pulmonary tuberculosis has shown a progressive decline in morbidity and mortality for more than a quarter of a century. Since 1921 the death rate has decreased from about 100 per 100,000 population to around 35 in 1946. The task of control, however, is still a difficult one. There are now at least half a million active cases in the population. In 1946 about 118,000 new cases were reported, and there were about 50,000 deaths from all types of tuberculosis. The campaign to eliminate this disease must be continued, using the newer methods for detection treatment and rehabilitation. BCG vaccine is being used on a limited scale and conservative opinion indicates that this procedure should probably be restricted to persons who are unusually exposed to the infection.

4. *Intestinal Infections.* The enteric diseases can all be prevented. Typhoid and the paratyphoid fevers can be controlled by vaccination. Except for veterans, however, the civil population has not been extensively immunized. Therefore, the civilian control of typhoid fever and of the other intestinal infections has been brought about largely through environmental sanitation, including improvements in the disposal of sewage and in the protection of water, milk and food. The reduction in typhoid has been most spectacular. In 1945 only 5,000 cases were reported in the United States, and during 1946, 41 American cities reported that there had not been a single death from typhoid fever in their populations during the previous two years.

The record of the other intestinal diseases is less satisfactory. Reports for 1945 show that the dysenteries, diarrhea and enteritis caused about 55,000 infections and more than 11,000 deaths. The continued appearance of these filth-borne infections is a national disgrace and calls for preventive action.

5. *Insect-borne Diseases.* The insect-borne diseases are also preventable, but they are by no means controlled. Malaria continues as a common cause of disability and chronic illness throughout the South, and the 61,000 cases reported in 1945 probably represent only a small proportion of the total infections. The gigantic wartime mosquito control program carried on by the armed services and the civilian public health agencies kept the army incidence rates for malaria contracted in this country at extremely low levels and caused an enormous decrease in civilian infections. This program should be continued.

In 1944 about 5,000 cases of murine typhus were reported, but the total incidence is believed to be much higher. Dengue fever is endemic in the South, and on occasions it causes extensive epidemics. Sylvatic plague exists among rodents over a wide area of the western states, and since no one can predict when it might become epidemic in man, it constitutes a potential menace. Plague vaccines are available, but the degree of protection which they afford is not known. Recent reports indicate that sulfadiazine, and possibly streptomycin, may be used effectively for treatment. This smoldering hazard should be removed.

Other important insect-borne diseases now endemic in the country include: Rocky mountain spotted fever, tularemia, and various types of virus encephalitis. The attack on these diseases should be directed toward the insect vectors and, when applicable, against rodent reservoirs of infection.

7. *Venereal Diseases.* The venereal diseases can also be prevented, but they continue to be a major health problem. In 1946 gonorrhea was the second of the 10 leading causes of disease, with more than a third of a million reported cases, and syphilis was third, with practically the same number of reported infections. In 1945 syphilis killed 14,000 people and was twelfth among the causes of death. The new methods of treatment with penicillin provide valuable weapons with which to intensify the attack on these diseases. The methods of prevention are known and these diseases should be controlled.

8. *The Chronic Degenerative Diseases.* Because of the increasing age of the population, the chronic degenerative diseases now rank as the most important causes of death, and are responsible for an enormous amount of sickness and disability. Last year the leading causes of mortality were: heart disease, cancer, cerebral hemorrhage and nephritis. According to Boas (1947) the most prevalent are rheumatism, heart diseases, arteriosclerosis and hypertension, and hay fever and asthma; while the most disabling are: nervous and mental diseases, rheumatism, heart diseases, and arteriosclerosis and hypertension.

Failure to control these diseases reflects the general ignorance concerning their underlying causes; and emphasizes the need for basic research aimed at the discovery of better methods of prevention, treatment and rehabilitation.

Such preventive services as are now available must be applied by the physician to the individual. They include early diagnosis of incipient disease through periodic physical examinations followed by correction of any defects found, and advice as to how to maintain normal health. This requires initiative on the part of the patient, a personal relationship between patient and physician, and adoption of the preventive viewpoint by the latter. Responsibility for the prevention of death from cancer, diabetes and other conditions in this group rests primarily with the medical practitioner and will continue to do so until better prophylactic methods can be found.

Official health agencies are also concerned with these problems and are becoming increasingly active in promoting adult health through education of

the public, and the initiation or provision of the diagnostic and other facilities required for better treatment and rehabilitation. At present health departments are actively engaged in such important fields as cancer control, industrial hygiene and mental hygiene.

9. *Smallpox.* A review of our remaining health problems would not be complete without mentioning smallpox. I have saved smallpox until last because it affords a spectacular example of the lag which still exists between the discovery of useful information and its practical application.

The value of vaccination has been recognized for a century and a half, but it has not been applied effectively in all parts of the United States. Consequently, the country is vulnerable to such invasions as occurred on the west coast in 1946, when the disease was imported from Japan and caused outbreaks in Washington and California; and again in 1947 when it was brought from Mexico into New York City. In both instances spread of the disease was stopped by extensive emergency vaccination programs. But this is an inefficient and costly way to control smallpox. In the New York episode the admission of a single case of smallpox into a modern hospital for contagious diseases was followed by the infection of at least 11 other persons, two deaths, a wave of popular hysteria that spread over the cities of the North Atlantic coast, and a mass vaccination program which involved at least 7 million people. This overtaxed the normal facilities for vaccine production and wasted millions of dollars. The whole affair could have been avoided if the unfortunate man who brought the infection from Mexico had been properly immunized before he left, or if his contacts in this country had all been protected by a satisfactory vaccination program.

This country's smallpox record is disgraceful. During the first quarter of the present century an average of over 40,000 cases was reported annually, and it was not until 1942 that the total fell below 1,000 cases per year. Even in 1945 and 1946 the annual totals were about 400 cases. Last year smallpox occurred in practically every country in the world and in many cases it reached epidemic proportions. At present, quarantine officers are alerted to prevent introduction of the disease from abroad. This would be unnecessary if our whole population was immune. If this country's experience with the prevention of smallpox affords an index of the efficiency with which all its other preventive measures are being practiced, there is ample room for improvement.

With the right sort of health education and the development of sound vaccination regulations, the continuing menace of smallpox can be eliminated in this country. In fact the disease could be controlled throughout the world within a relatively short period of time. An example of what can be done is afforded by the recent vaccination of the entire Japanese nation—a total of 78 million people—as a part of the comprehensive health program inaugurated and directed among the civilians of Japan by the United States Army.

In this brief review, I have mentioned only a few of the health problems with which we are faced today. We can all think of others—such as those

posed by occupational and industrial hazards, the high accident rates, nutritional deficiencies, the housing shortage, the need for rehabilitation, the pollution of our rivers with sewage and industrial wastes, and the need to protect our national water supplies.

Moreover, if one is to be realistic, it must be assumed that new problems may appear without warning next year or next week. For example, pandemic influenza will undoubtedly return some day, and plans should be made to meet it. Also, the country will probably be invaded again by yellow fever from Africa or South America, or by cholera or virulent plague from India or China, or by other exotic diseases from other countries, and we must be prepared to recognize such diseases and prevent their spread. Finally, we may be confronted some day with the still unknown hazards of atomic or biological warfare waged—not in some far-off land, but—in the streets of San Francisco, Chicago, New York and Washington.

Conclusion

Now that we have defined preventive medicine broadly as the sum total of all those activities required to prevent disease and to keep well people well, have indicated its past contribution to the nation's health, and have pointed out some of the numerous health problems that remain unsolved, it is time to consider what can be done to meet the present challenge.

I have no intention of trying to tell this audience how to organize a national program of health. We all know that there is an important job to be done which will require the coördinated application of the best services available in both curative and preventive medicine. We also know from experience during the recent war what great potentialities for unselfish, united service exist among the scientists who make up the professions of medicine and public health, and I am sure we all have faith in their ability to meet this challenge.

It is obvious that immediate action should be taken to apply the knowledge now at hand to the eradication of preventable sickness, to the elimination of unnecessary death and disability, and to the rehabilitation of the physically and mentally unfit. It is equally apparent that adequate community health services and first class medical and surgical care should be made available to every man, woman and child in this country—not because of any idealistic concept that man has a parasitic right to demand health, but for the very practical reason that they are Americans, and their health is essential to the future strength and security of the nation.

It is also obvious that plans should be made for the future improvement of these services through better education and more research. The instruction in our medical and dental schools should be improved and geared up to Osler's vision of preventive medicine as the medicine of the future. Better and more adequate training should be provided in our schools of public health, and the principles of health should be taught to all Americans. Basic

medical research should be intensified and amply supported in order to develop better methods with which to control disease and promote health. It seems ridiculous that political considerations have held up the establishment of the long-delayed National Research Foundation. But you are familiar with these things, and it is not necessary to discuss them further. Before closing, however, I do wish to emphasize the fact that what we really need in order to meet the challenge of the future, is united, objective leadership within the ranks of medicine and public health.

With such leadership, the task should not be too difficult, for the people of this country sincerely want health. The experience of the recent war impressed them with the importance of preventive medicine. Strong tides of popular interest in public health are now running through this country and the people are ready to take whatever steps may be required to release themselves and their children from the unnecessary burden of preventable sickness and death. This rising tide of interest is reflected in the confusing deluge of bills which have recently been presented to the Congress in the hope of providing a more effective national health program. The unsatisfactory nature of many of these bills is indicated by the violent disagreements they have aroused within the ranks of the professions of medicine and public health. Such controversies must be even more confusing to the layman than they are to many of us. He must wonder why his medical leaders do not sit down together and draw up the blueprint for a sound and realistic health program which they can agree upon, and which is suitable for operation in our democratic society of free men. I am sure we all agree that the man in the street and the lawmaker do have a right to expect this sort of united leadership.

There is no question that the great body of unselfish men and women included in the professions of medicine and public health are vitally interested in making better health available to the people; also, that they alone are qualified to make sound plans by which to accomplish this. However, from the present chaotic status of health legislation, it is obvious that we are split into opposing groups that have not been able to agree—a situation that must remind the layman of current world politics or of Nero's fiddling in ancient Rome. This disturbing spectacle is decreasing the prestige of our professions, and, unless corrected, our lawmakers may be expected to adopt the attitude that if the leaders who have the primary responsibility for health cannot get together, they will seek leadership elsewhere.

It seems to me that a matter of such vital importance as the nation's health program should not be planned in a haphazard way, or by the hurried calling of emergency meetings of unrepresentative groups composed largely of laymen. I believe that health is sufficiently important to warrant calm, objective planning on a continuing basis by experts who represent the best available professional skill and judgment. I also believe that such experts should be able to agree on certain things that are needed and can be done

now, and that they should continue to seek a realistic solution for problems on which there is honest disagreement.

With this objective in mind, I wish to suggest that a permanent national advisory and planning council on health be organized with broad, official representation, including members elected from the American College of Physicians, the American College of Surgeons, the American Medical Association, the American Public Health Association, and all the other leading organizations competent to deal with medicine and public health. Such a representative council could concern itself with long-term planning for: (1) the improvement of teaching in medicine and public health; (2) the stimulation of medical research; and (3) the development of a sound program for the education of the public in the principles of health. In addition, this council could act in an advisory capacity to the government in all matters of health legislation.

In view of the fact that the American College of Physicians is composed of a large group of the elder statesmen in American medicine, it would seem appropriate for this distinguished organization to initiate the formation of such a council.

BIBLIOGRAPHY

BLAKE, F. G.: Some recent advances in the control of infectious disease, Rhode Island Med. Jr., 1945, xxviii, 409.

EMERSON, H.: The unfinished job of essential public health service, Am. Jr. Pub. Health, 1948, xxxviii, i, 164.

EMERSON, H.: Local health units for the nation, Am. Jr. Pub. Health, 1947, xxxvii.

FISHBEIN, M.: A history of the American Medical Association, 1947, W. B. Saunders Co., Philadelphia, Pennsylvania.

FRANCIS, T.: A consideration of vaccination against influenza, Milbank Memorial Fund, Quarterly, 1946, xxv, 5.

GREGG, A. G.: Transition in medical education, Jr. Assoc. Am. Med. Coll., 1947, iv, 22.

LEAVELL, H. R.: The teaching of preventative medicine, Jr. Assoc. Am. Med. Coll., 1947, iv, 210.

PARRAN, T.: Surmounting obstacles to health progress, Jr. Am. Pub. Health Assoc., xxxviii, 1, 168.

PARRAN, T., and BOUDREAU, F. G.: The world health organization cornerstone of peace, Am. Jr. Pub. Health, xxxvi, 1, 267.

Metropolitan Life Insurance Co., Statistical Bulletin, xxviii, 10, 2.

REED, L. J.: Changing problems growing out of the change in composition of the population, Jr. Am. Pub. Health Assoc., 1948, xxxviii, 160.

RUSSELL, W. L.: The national mental health act, Am. Jr. Psychiat., 1946, ciii, 417.

SMILLIE, W. S.: Preventive medicine and public health, 1946, The Macmillan Co., New York.

STIEGLITZ, E. J.: A future for preventive medicine, 1945, The Commonwealth Fund, New York.

WINSLOW, C.-E. A.: Poverty and disease, Jr. Am. Pub. Health Assoc., xxxviii, 173.

WINSLOW, C.-E. A., BOUDREAU, F. G., and HUME, E. H.: Uniting the nations for health, Commission to Study the Organization of Peace, American Association for the United Nations, Inc., 1947, New York.

PRELIMINARY REPORT ON THE BENEFICIAL EFFECT OF CHLOROMYCETIN IN THE TREATMENT OF TYPHOID FEVER*

By THEODORE E. WOODWARD, M.D., JOSEPH E. SMADEL, M.D., HERBERT L. LEY, JR., M.D., *Baltimore, Maryland,* and *Washington, D. C.,* RICHARD GREEN, M.D., and D. S. MANKIKAR, M.D., *Kuala Lumpur, Federation of Malaya*

A NEW antibiotic Chloromycetin has been clinically tested in the treatment of typhoid fever and has been found to exhibit significant chemotherapeutic effects. A description of the results in 10 cases is submitted as a preliminary report.

Chloromycetin is a crystalline substance obtained through processes of concentration and purification of cultures in liquid media of a Streptomyces sp. originally isolated by Burkholder,† and shown by him to possess anti-bacterial activity. Ehrlich and associates [1] in the Research Laboratories of Parke, Davis and Company carried out studies of the antibiotic activity of this Streptomyces which led to preparation of the crystalline antibiotic compound to which Ehrlich gave the name Chloromycetin.

Chloromycetin is a neutral compound containing both nitrogen and nonionic chlorine. In distilled water it withstands boiling for five hours, and in aqueous solutions over the pH range 2 to 9 is unaffected by standing at room temperature for more than 24 hours. Its solubility in water at 25° C. is about 2.5 mg./ml. and it is reported as very soluble in propylene glycol, methanol, ethanol, butanol and acetone. It is well absorbed from the gastrointestinal tract. Serum levels of the drug after oral administration have been found to be comparable to those obtained by parenteral injection. Present evidence indicates that the antibiotic is fairly rapidly excreted or inactivated.

Reported toxicity experiments on animals [2] indicate that when given intravenously in mice and intramuscularly in dogs Chloromycetin is well tolerated in single doses up to 100 mg. per kg. of body weight. Larger doses have been tolerated orally. On chronic parenteral administration in dogs the development of anemia has been noted. Variations in the white blood cells, and disturbance in hepatic or renal function have not been observed.

Initial studies of the antibiotic spectrum of Chloromycetin in vitro and in vivo in animals have been published.[2, 3] These investigations have indicated outstanding effectiveness in rickettsial infections of chick embryos and mice. In addition Chloromycetin has been shown in vitro to be active against gram negative bacteria and *Borrelia recurrentis* and moderately active against *Mycobacterium tuberculosis* and gram positive bacteria.

Reports on the use of Chloromycetin in the treatment of human infections, up to the time of writing, have been confined to its use in epidemic typhus [4, 5] and in

* Received for publication May 16, 1948.

From The Department of Medicine, University of Maryland, School of Medicine; The Department of Virus and Rickettsial Diseases, Army Medical Department of Research and Graduate School; the Commission on Immunization of the Army Epidemiology Board; and from The Institute for Medical Research, Kuala Lumpur, Malaya.

† Dr. Paul R. Burkholder, Osborn Botanical Laboratory, Yale University.

scrub typhus.[6] In both of these rickettsial infections Chloromycetin has demonstrated marked therapeutic effectiveness.

In the course of an investigation of the chemotherapeutic value of Chloromycetin in the treatment of scrub typhus fever on the Malayan peninsula in the vicinity of Kuala Lumpur, the authors encountered numerous cases of typhoid fever which is endemic in this area, especially in the native population. Typhoid fever in this area tends to be of a clinically severe type, the febrile course not infrequently running to six or seven weeks.

Advantage was taken of this opportunity to test the efficacy of Chloromycetin in the treatment of this important type of enteric disease. The present report deals with the results obtained in 10 cases of typhoid treated with Chloromycetin. Chloromycetin used in this work was supplied by the Research Division of Parke, Davis and Company. Observations made on eight non-treated cases serve as a control.

The diagnosis in the 10 treated cases was confirmed by a blood culture positive for *Eberthella typhosa* prior to the initiation of specific therapy.

Chloromycetin was administered orally. The initial dose in each case was 50 mg./kilo of body weight. Thereafter 0.25 gm. was given every two hours until the temperature was normal and the same dose every three to four hours thereafter during the first five days of normal temperature. The total dosage per patient averaged 19.1 grams given over a period of 8.1 days. The drug was well tolerated and no clinical evidences of toxicity were observed.

The blood level for Chloromycetin was followed throughout the course of treatment. The blood concentration of the drug during the first 24 hours of therapy was of the order of 40 to 80 gamma per c.c. and during the subsequent three days remained at a level of 20 gamma per c.c. Workers at the research division of Parke, Davis and Company had previously shown that *E. typhosa* is inhibited by concentration of Chloromycetin of approximately one-quarter gamma per c.c. when the 50 per cent end-point technic is applied to fluid culture. Further details on blood concentrations and on the sensitivity of the typhoid organisms will be included in a later report.

Course of the Disease in Treated Cases: Cases in the first two weeks of their febrile course were selected for specific treatment. The majority of the 10 cases were started on the drug about the tenth day of their fever. The mean duration of known fever prior to treatment in the 10 cases was 9.5 days. The course of the disease after the start of Chloromycetin administration was followed by observations on the clinical condition, the duration of fever and the results of repeated blood, stool and urine cultures.

Evidence of improved general condition and lessened toxicity was usually apparent within 24 hours after the start of specific treatment, and increasingly thereafter. In the first seven cases the temperature reached permanent normal levels after three days of treatment. The mean in the 10 cases for

the duration of fever after beginning chloromycetin treatment was 3.5 days. The response to therapy in a characteristic case is represented in figure 1.

In eight of the 10 cases blood cultures were taken daily for five days following the initiation of treatment.* All of these blood cultures remained sterile. In two of these eight cases blood cultures were taken two, four and eight hours after the initial dose of Chloromycetin. These cultures likewise remained sterile. After the fifth day from the beginning of therapy, in view of the patients' normal temperatures, blood cultures were not taken except in those instances (vide in figure) in which a positive stool culture was obtained. The three blood cultures taken because of this indication proved negative.

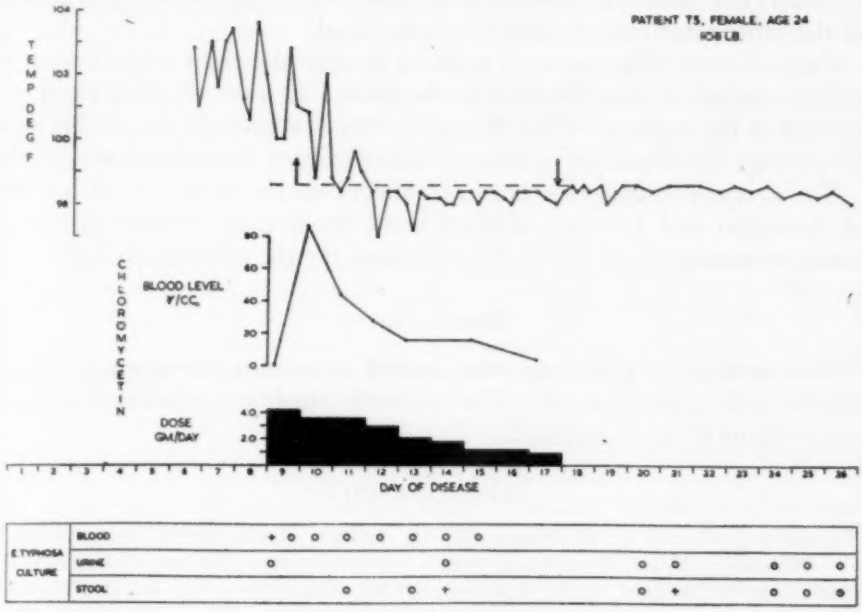

FIG. 1.

Because of the conditions under which this study was carried out, stool cultures could not be obtained on any regular schedule. However, no patient was discharged without three consecutive negative stool cultures having been recorded. Positive stool cultures after the termination of Chloromycetin treatment were observed in three instances in two patients during their convalescence. In one of the patients the stool specimen obtained on the seventeenth day after the institution of therapy was positive. In the second patient positive stool cultures were recorded on the fifth and twelfth days. Repeated stool cultures thereafter in these two patients were negative.

Urine cultures before the beginning of specific therapy, during therapy and in convalescence were consistently negative.

* In two cases it was not feasible to obtain daily blood cultures.

Relapses: Two of the 10 patients developed relapses with bacteremia occurring after afebrile periods of 10 and 16 days respectively. In both instances the recurrent infection responded promptly (three and two days) to a second course of Chloromycetin. It is of interest that the organisms isolated during the recurrence were as sensitive to Chloromycetin when tested in vitro as were those isolated initially.

Complications: Two serious complications, other than the recurrences noted above, were encountered among 10 patients. These consisted of intestinal perforation in one case, occurring on the second day of normal temperature; and, in a second case, massive intestinal hemorrhage developing in the fourth afebrile day. Following a more or less stormy course both recovered: one after supplementary therapy with streptomycin and penicillin and the other after transfusions of whole blood.

Control cases: The course of typhoid fever in the eight control cases is in striking contrast to that observed in the treated series. Of these eight cases, one died of the severity of the disease on the seventeenth day of his illness. The average total duration of fever in the remaining seven cases was 35 days.

The average treated case began treatment on the ninth day of his illness and thereafter had 3.5 days of fever while the average control case not receiving treatment on the ninth day ran fever for the ensuing 26 days.

Conclusions

The antibiotic, Chloromycetin, exerts a specific therapeutic effect in patients with typhoid fever. The optimal schedule for administering the drug remains to be determined.

BIBLIOGRAPHY

1. Ehrlich, J., Bartz, Q. R., Smith, R. M., Joslyn, D. A., and Burkholder, P. R.: Chloromycetin, a new antibiotic from a soil actinomycete, Science, 1947, cvi, 417.
2. Smith, R. M., Joslyn, D. A., Gruhzit, O. M., McLean, I. W., Jr., Penner, M. A., and Ehrlich, J.: Chloromycetin: biological studies, Jr. Bact., 1948, lv, 425–447.
3. Smadel, J. E., and Jackson, E. B.: Chloromycetin, an antibiotic with chemotherapeutic activity in experimental rickettsial and viral infections, Science, 1947, cvi, 418.
4. Smadel, J. E., León, H. E., Ley, H. L., Jr., and Varela, G.: Chloromycetin in the treatment of patients with typhus fever, Proc. Soc. Exper. Biol. and Med. In press.
5. Payne, E. H., Knaudt, J. A., and Palacios, S.: Treatment of epidemic typhus with Chloromycetin, Jr. Trop. Med. and Hyg., 1948, li, 68.
6. Smadel, J. E., Woodward, T. E., Ley, H. L., Jr., Philip, C. B., Traub, R., Lewthwaite, R., and Savoor, S. R.: Chloromycetin in the treatment of scrub-typhus. (Read before the International Congress for Tropical Disease, Washington, D. C., May 11, 1948.) Science. In press.

CASE REPORTS

THE TOXICITY OF BENADRYL: REPORT OF A CASE AND REVIEW OF THE LITERATURE*

By BERNARD A. SACHS, Capt., M.C., A.U.S.,† *Baltimore, Maryland*

BENADRYL ‡ (b-dimethylaminoethyl benzhydryl ether hydrochloride) is an anti-histaminic substance synthesized by Rieveschl and Huber and first reported by Loew, Kaiser and Moore.[37] Ever since the first clinical report by Curtis and Owens [1] toxic reactions have been mentioned frequently and prominently. A recent instance led us to review the literature and attempt to ascertain the frequency and character of toxic reactions and the relation of reaction to dosage. Toxic reactions have been variously termed side effects, side reactions, side actions, untoward reactions or untoward effects and these terms will be used interchangeably.

CASE REPORT

The patient, a 28 year old white officer, first reported to a dispensary on October 24, 1946 with symptoms of prostatitis. He had an enlarged, tender prostate. On October 26 he received four 100,000 unit injections of penicillin one hour apart and sulfadiazine, one gram four times daily. The next day the sulfadiazine was discontinued because the patient developed a few mild urticarial lesions which soon became generalized. One day later the urticaria spontaneously disappeared. On November 1 he developed joint pains, swelling of the wrists and ankles and mild urticaria of the face and neck. This was treated with ephedrine capsules and frequent injections of epinephrine. Because the lesions progressively increased in severity and itched badly he was admitted to a station hospital on November 4, when he had marked urticaria of the face with large wheals over the neck, and periorbital edema closing his eyes. No other lesions were noted. The leukocyte count was 7600 with 61 per cent neutrophiles, 38 per cent lymphocytes and 1 per cent eosinophiles; hemoglobin was 15 grams and the urine, normal.

The patient was given 10 c.c. of 10 per cent calcium gluconate intravenously and 50 mg. of benadryl three times a day with some initial improvement. However, on November 11 one week after admission, the urticaria became more severe and involved the thorax and upper extremities. Furuncles were noted on his right forearm to which hot saline packs were applied; serous bullae soon developed in these areas. His temperature, which had previously been 100° or less, rose to 101.2° and pulse to 100. A penicillin skin test was read as four plus. The patient was given four grams of sulfadiazine because it was felt he had secondary infection of the lesions. The benadryl was continued. On November 12 the joint pains increased, the urticaria became very severe and some erythema multiforme-like lesions developed. He was then transferred to this hospital.

* Received for publication April 21, 1947.
From the Regional Station Hospital, Fort Belvoir, Virginia.
† At present visiting Fellow in Medicine, The Johns Hopkins University School of Medicine.
‡ Diphenhydramine hydrochloride, New and Non-official Remedies, 1947.

On admission the patient complained of painful shoulder, elbow and interphalangeal joints bilaterally as well as "nervousness." One year before admission he had received penicillin for pneumonia but after two days this was discontinued and sulfonamide therapy initiated. He did not recall a skin eruption, drug fever, joint pains or urinary symptoms occurring at that time. He had no previous allergy. A maternal uncle had bronchial asthma.

His temperature was 101.2°, pulse 90 and respirations 24. (Blood pressure was not taken on admission because of edema but was subsequently 128 mm. Hg systolic and 64 mm. diastolic.) There were severe, massive, indurated wheals one to five centimeters in diameter with erythematous centers and irregular, elevated peripheries most numerous over the upper extremities and thorax, and confluent about the neck. Those on the dorsum of the hand had purplish centers. The patient had swelling and scaling of the face, especially the periorbital regions, and edema of the arms and hands with swelling of the interphalangeal joints bilaterally. Numerous confluent serous bullae were noted on the flexor surface of the right forearm. There were crepitant inspiratory râles over both lung bases posteriorly, a slight dry cough, and moderately tender axillary lymph nodes bilaterally.

The leukocyte count was 14,800 with 81 per cent neutrophiles and 19 per cent lymphocytes. His urine and serologic test for syphilis were normal. Roentgen-ray of the chest showed a patchy density in the left base approximately three centimeters in length.

Soon after admission the patient was given 25 mg. (2.5 c.c.) of benadryl intravenously and 20 minutes later 10 mg. (1 c.c.) with no change in the pruritus, joint pains, skin lesions or periorbital edema. The only result noted was sudden drowsiness. That day he also received a total of 250 mg. of benadryl by mouth. The following day (November 13) the patient voluntarily stated he felt better and the itching had gone. However, the lesions objectively were of the same severity and had the classical appearance of urticaria with circinate and gyrate formations over the face, neck, shoulders, arms and back. Because of the dramatic results obtained in other patients,* [38] an infusion of one gram of procaine in 1000 c.c. of 5 per cent glucose in distilled water was given over a period of three and three-quarters hours. Well circumscribed lesions were measured frequently before, during and after the infusion and no change was noted, subjectively or objectively. Since there was no improvement, beginning on the evening of November 13 the patient was given 100 mg. of benadryl every four hours. On November 14 some of the lesions on the thorax showed central clearing but the lesions on the back became more confluent. He also developed many wheals on his abdomen and a few lesions on his legs, but the edema of the hands decreased somewhat. By November 16 the joint pains had markedly decreased, the edema of the face had gone down considerably and the urticaria had completely disappeared from the back and legs. The patient continued to complain of "nervousness" as well as drowsiness and stated that for the past few days he had noticed subjective dizziness upon awakening and dryness of the mouth. Later this day (after having received 1500 mg. of benadryl in two and one-half days) the patient claimed mustard was being squirted on him from the walls and ceiling. He stated he smelled mustard and made other irrational statements. He telephoned the military police in reference to an allegedly stolen car and later asked the nurse to call the undertaker. During the day he appeared suspicious of all food and drink and when questioned replied that someone had been putting laxatives in them. His speech became jerky and rapid and a definite tremor of the extended hand was noted. At all times he was well oriented as to time, place and person. Because of these signs

* One patient treated here had severe urticaria due to sensitivity to penicillin. This disappeared at once after an infusion of procaine. Some days later he had a recurrence of urticaria which responded very quickly to intravenous benadryl and did not return.

benadryl was discontinued on the evening of November 16 and he was given one gram of chloral hydrate as a sedative. The following morning the patient was quite rational and did not remember any of the previous day's unusual happenings. On November 17 the urticaria was completely gone. On November 18 a roentgenogram of the chest was clear. Subsequent blood studies revealed a leukocyte count of 7500 with 72 per cent neutrophiles, 24 per cent lymphocytes and 4 per cent eosinophiles.

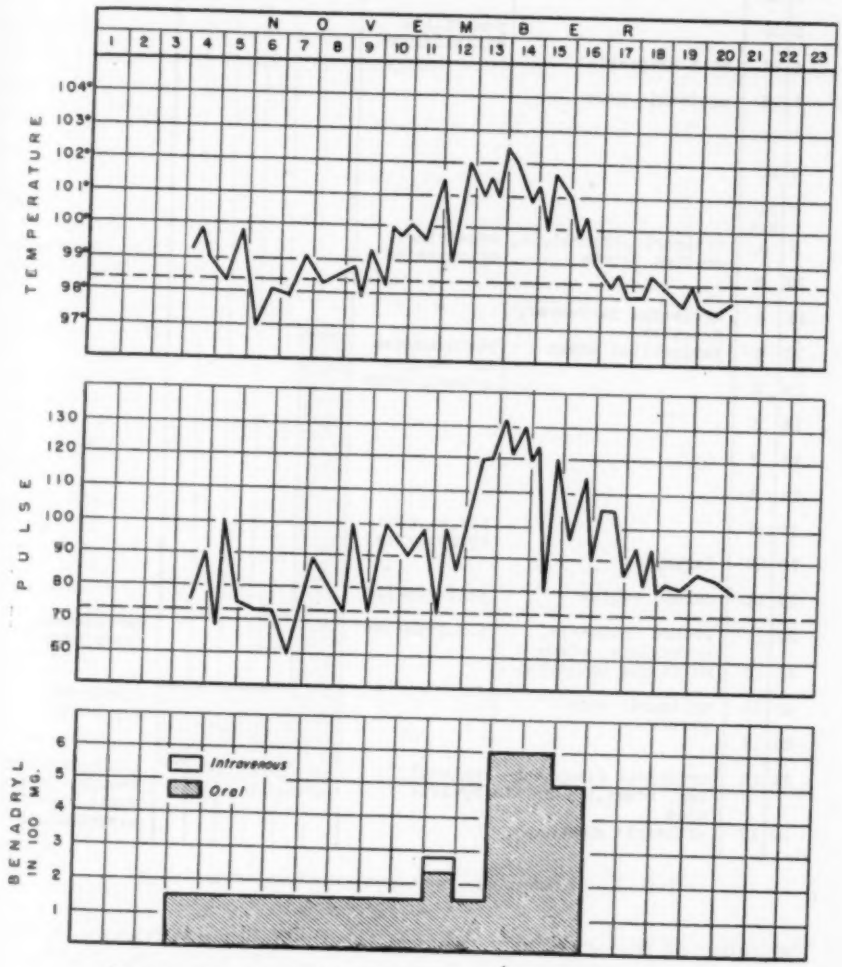

FIG. 1. Case report: temperature, pulse, benadryl dosage.

His course had been marked by an irregular temperature as high as 102.6° and tachycardia for the first five days (figure 1). He was asymptomatic after November 17. Before discharge on November 23 he stated that he recalled being "confused" on occasion during therapy. The relation of symptoms to benadryl dosage is illustrated by figure 2.

DISCUSSION

A. Case. A case is reported in which severe urticaria, edema and arthralgia resulted, probably due to either penicillin or sulfadiazine. It is felt that penicillin

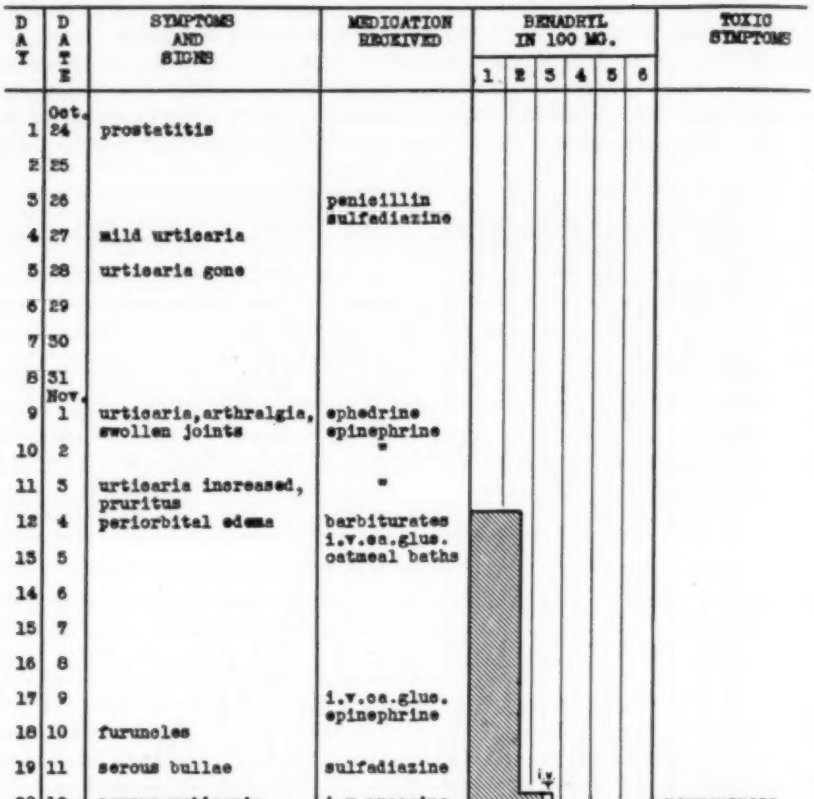

FIG. 2. Case report: time-dose-symptom relationships.

was the cause of the sensitivity reaction for the following reasons: history of interruption of penicillin therapy during a previous hospitalization for pneumonia, four plus penicillin skin test, and the nature of the reaction. The patient was not relieved by ephedrine, epinephrine, calcium gluconate, intravenous benadryl or intravenous procaine. During eight days of oral benadryl at a dose of 150 mg. a day his lesions became progressively worse. The urticaria, edema and arthralgia cleared while benadryl was given at a dose of 600 mg. a day for two and one-half days. However, during this time he developed severe toxic reactions including dizziness, dryness of the mouth, visual and olfactory hallucinations, mental confusion, tremor, and jerky, rapid speech. It was necessary to discontinue the drug because of the severe reaction; the following morning the

patient was perfectly rational and normal. Hallucinations and jerky, rapid speech are reported for the first time.

B. Frequency of Reactions. Side reactions occurred in 46.4 per cent of 1210 patients.[1–8, 10, 11, 13–18, 20] In the 836 patients concerning whom adequate figures are given, [1–4, 6–13, 15–17, 20] drowsiness, found in 34.2 per cent, was the most frequently encountered toxic reaction. The soporific effect varies from a mild drowsy sensation to a deep slumber lasting 18 hours. Dizziness was the second most common reaction and was found in 14.1 per cent. Dryness of the oral cavity was found in 5.6 per cent, nausea in 2.6 per cent and nervousness in 2.3 per cent of the 836 patients. These are the most common reactions. Other reactions are noted in table 1. Asthma has been reported in 11 patients. [4, 5, 7, 30]

TABLE I

Classification of Toxic Reactions Encountered with Benadryl*

I. Neuro-psychiatric
- Drowsiness[1–19, 21–30, 40, 41]
- Dizziness[1–5, 7–9, 11, 13, 16, 18, 19, 22–24, 26–28, 30]
- Nervousness[2, 5–8, 10, 13, 23, 26, 27, 28, 30]
- Weakness[1, 3, 5, 7, 11, 13]
- Fatigue[2, 9, 13]
- Faintness[3, 7, 8, 13, 25]
- Paresthesia[4, 5, 11, 15, 40]
- Difficulty in coördination[2, 15, 18, 30]
- Mental confusion[5, 8, 18, 26, 39, 41]
- Headache[16, 29, 40]
- Amnesia[5, 9]
- Lassitude[24, 37]
- Choking[9, 19]
- Slurred speech[39, 40]
- Malaise[10, 42]
- Disoriented[41, 42]
- Tinnitus[2, 16]
- Stupor[5]
- Narcolepsy[5]
- Somnambulism[5]
- Exhaustion[5]
- Irritability[5]
- Giddiness[25]
- Slow speech[40]
- Athetoid movements[39]
- Acute melancholia[40]
- Peripheral neuritis[40]
- Insomnia[7]
- Tremor[8]
- Sense of relaxation[2]
- Mental lethargy[40]
- "Walking on air"[16]
- "All gone feeling at pit of stomach"[19]
- Acute hysterical reaction (i.v.)
- Apprehension (i.v.)
- Hallucinations (case report)
- Jerky rapid speech (case report)

II. Alimentary
- Dry oral cavity[2, 3, 5, 6, 12, 16, 18, 19, 22–27, 30]
- Nausea[2, 4–6, 11, 12, 18, 29, 42]
- Vomiting[4, 6, 11–13, 16, 17]
- Epigastric distress[3, 20]
- Bad taste[2, 5]
- Diarrhea[2, 13]
- Abdominal cramps[7]
- Indigestion[5]
- Heartburn[42]
- Sore tongue[5]
- Constipation[2]
- Taste like chloroform (i.v.)

III. Cardiovascular
- Orthostatic hypotension[9, 19]
- Hypotension[11]
- Palpitation[5, 7, 42]
- Facial edema[6, 40]
- Elevated pulse[9]
- Excessive perspiration[3]
- Cold extremities[5]
- Vasospasm of fingers[27]
- Pallor[5]
- Collapse[5]
- Shocklike reaction[42]
- Hot flashes[5]
- Bleeding tendency ?[2]
- Chills (i.v.)

IV. Respiratory
- Asthma[4, 5, 7, 30]
- Dry nose[7]

V. Genito-urinary frequency[2, 11]
- Discomfort[11]

VI. Muscular, aching,[1, 10, 11, 21] twitching[4, 39]
- Low back pain (i.v.)

VII. Ocular
- Blurring of vision[2, 5, 9, 19, 28, 30]
- Difficulty in ocular accommodation[10, 12]
- Dilated pupils[5, 9]
- Photophobia[10]
- Dimmed vision[42]

VIII. Miscellaneous
1. Generalized pruritus (i.v.)
2. Aggravation of allergic symptoms[5]

*Symptoms designated (i.v.) were seen only after intravenous administration.

Four of these had aggravation of existing asthma [5] and four had a previous idiosyncrasy to acetylsalicylic acid.[7, 30]

Toxic reactions appear to be more frequent when benadryl is given intravenously, occurring in 65 per cent of 43 patients [2, 9, 15] (table 2). Again drowsiness and dizziness are the prominent symptoms. The reactions encountered are, in general, more acute in onset, more severe, and of shorter duration. Weakness is seen much more frequently when the drug is given by vein. Six reactions ("acute hysterical reaction," chills, generalized pruritus, low back pain, taste like chloroform and apprehension) have been described only as a result of intravenous administration.

TABLE II

Toxic Reactions with Intravenous Benadryl

	Author			Total	
	McElin and Horton[2]	McGavack, Elias and Boyd[9]	Lofstrom and Nurnberger[15]	Number	Per Cent
Dosage in mg.	10–120 in 10 min.	20–30	50–150		
No. of Pts.	26	10	7	43	100
No. of Pts. with Reactions	18	3	7	28	65
Reactions:					
Dizziness	12	1	4	17	39
Drowsiness	9	1	6	16	37
Weakness	0	1	6	7	16
Dry mouth	3	0	0	3	7
Tingling in legs	2	0	0	2	5
Chills or chilliness	1	1	0	2	5
Headache	0	2	0	2	5
Tinnitus	1	0	0	1	2
Low back pain	0	1	0	1	2
Pruritus	1	0	0	1	2
Taste like chloroform	1	0	0	1	2
Faintness	1	0	0	1	2
Hysterical reaction	1	0	0	1	2
Nervousness	1	0	0	1	2
Seasickness	0	1	0	1	2
Pallor	0	1	0	1	2
Sweating	0	1	0	1	2
Sl. decrease temperature	0	1	0	1	2
Vision hazy	0	0	1	1	2
Walking unsteady	0	0	1	1	2
Apprehension	0	0	1	1	2

Therapy was discontinued, at the will of the patient or physician, in 6.4 per cent of 1929 * patients.[1, 3–8, 11–13, 16–18, 28, 39, 40, 42] If recovery from acute lesions was not so prompt this fraction would be greater.

C. Character of Reactions. Numerous untoward reactions have been described and may be roughly classified into eight groups: (1) neuro-psychiatric; (2) alimentary; (3) cardiovascular; (4) respiratory; (5) genito-urinary; (6)

* The total number of patients in the series reviewed.

muscular; (7) ocular; and (8) miscellaneous (table 1). Toxicological studies in dogs reveal that high doses of benadryl cause ataxia, gastrointestinal reactions, nervousness and hyperesthesia of skin. Lethal doses in mice and rats (in which the oral LD50 is 167 and 545 mg. per kilogram respectively) produce violent excitement, convulsions and respiratory failure.[32] Intravenous injections in dogs produce hypotension of diphasic alterations in blood pressure depending upon the rapidity of injection.[33] Orthostatic hypotension and sustained hypotension have been observed in man.[9, 11, 19, 40] No alterations were noted in blood counts, blood chemistries and numerous other laboratory procedures repeated over long periods of time.[2, 9] No cumulative toxic reactions were noted in patients taking the drug for as long as seven months.[1]

Except perhaps for the occurrence of asthma after benadryl in patients sensitive to acetylsalicylic acid (each of these drugs contains a coal tar radical), the mechanism of toxic reactions has not been explained adequately.[7, 30]

D. Relation of Symptoms to Dosage. It may be stated only generally that untoward reactions are more common with higher doses. Profound reactions have occurred with a single 50 mg. dose, and 600 mg. has been given in one day without toxic effect.[5, 13] It appears, however, that the most severe toxic reactions occur most often with higher doses. Toxic reactions occur on some occasions and not on others with the same dosage in the same patient.[5] No correlation has been apparent between the occurrence of toxic reactions and either the nature of the disorder for which the drug was given or the character of the therapeutic result. There appears to be no correlation between the type of reaction encountered and the size of dose.

E. Control of Toxic Reactions. Side reactions can be made minimal in severity by reducing the dosage, giving the drug after meals, ordering the initial dose in the evening and prescribing stimulants such as black coffee, caffeine, ephedrine or amphetamine sulfate.[4, 5, 12] The last is the most effective stimulant.[6, 11, 14] If the untoward effect is mild the patient may continue at the initial dosage. A large number of patients develop tolerance and the untoward effect gradually disappears.[7, 9, 16] If the side reactions are severe, benadryl should be discontinued. The toxic effects disappear in from one to several hours after stopping the drug.[1, 9, 18, 19 and present case report] Only one case of prolonged toxic effect after cessation of therapy has been reported.[40] Addiction, in those who react with sleepiness, has not been encountered. Late side reactions, occurring for the first time after several months of therapy, have been reported by one author.[18] Benadryl should not be given in conjunction with sedatives or hypnotics because of the additive effect.[12, 30]

The patient must be warned about the possible toxic reactions since these may bring about other effects varying from mere embarrassment to severe injury.[30] These are usually due to the soporific side action. The drug may be a serious hazard when used by persons operating automobiles or machinery, or walking unescorted through traffic.[4, 29, 30, 31]

In evaluating the therapeutic use of benadryl fairly, one must consider the reactions discussed above. Although many of the reactions have been severe, the great majority have been mild. With one exception,[40] all of the reactions, regardless of severity, have been relieved shortly after discontinuing the drug or decreasing the amount given. This brief duration of reactions, associated

with the lack of cumulative drug effect greatly lessens the seriousness of benadryl toxicity.

Conclusions

1. Toxic reactions from the therapeutic use of benadryl are common, occurring in 46.4 per cent of patients.

2. With intravenous therapy, toxic reactions are more frequent occurring in 65 per cent of patients, are more acute, somewhat more severe and of shorter duration.

3. The drug was discontinued because of toxic reactions in 6.4 per cent of 1929 patients.

4. Toxic reactions are unpredictable, occurring with small doses and occurring on some occasions and not on others at the same dosage in the same patient. In general, untoward reactions are more commonly encountered with high doses of the drug.

5. Toxic reactions, regardless of severity, are relieved shortly after discontinuing the drug. There is no evidence of cumulative toxic effect. Because of these two facts it must be concluded that the toxicity of benadryl, despite the frequency of side reactions, is low.

Summary

The chief limiting factors in the use of benadryl are the toxic reactions. A case of urticaria, edema and arthralgia probably due to penicillin sensitivity is reported. This patient did not respond to 150 mg. of benadryl a day but became completely well with a daily dose of 600 mg. On this high dosage the patient developed many untoward reactions including hallucinations and jerky, rapid speech which are reported for the first time.

The frequency of toxic reactions with oral and intravenous benadryl is cited. The five most common reactions are, in order of frequency, drowsiness, dizziness, dry oral cavity, nausea and nervousness. There are numerous variations in symptomatology. Some reactions have occurred only with intravenous use of the drug. The relation of symptoms to dosage is discussed. Mention is made of hazards that may result from toxic reactions. Measures for avoiding or minimizing untoward reactions are noted. The mechanism of these reactions remains obscure.

BIBLIOGRAPHY

1. Curtis, A. C., and Owens, B. B.: B-dimethylaminoethyl benzhydryl ether HCl (benadryl) in treatment of urticaria, Univ. Hosp. Bull., Ann Arbor, 1945, xi, 25; Arch. Dermat. and Syph., 1945, lii, 239.
2. McElin, T. W., and Horton, B. T.: Clinical observations on the use of benadryl: a new antihistaminic substance, Proc. Staff Meet., Mayo Clin., 1945, xx, 417.
3. O'Leary, P. A., and Farber, E. M.: Benadryl in the treatment of urticaria, ibid., 1945, xx, 429.
4. Waldbott, G. L.: Clinical results with benadryl, Jr. Allergy, 1946, xvii, 142; New antihistaminic drugs in allergic diseases, Jr. Mich. Med. Soc., 1946, xlv, 1051.
5. Levin, S. J.: B-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl). Its use in allergic diseases, Jr. Allergy, 1946, xvii, 145.

6. Koelsche, G. A., Prickman, L. E., and Carryer, H. M.: The symptomatic treatment of bronchial asthma and hay fever with b-dimethylaminoethyl benzhydryl ether hydrochloride, ibid., 1946, xvii, 151; Proc. Staff Meet., Mayo Clin., 1945, xx, 432.
7. Eyerman, C. H.: Clinical experiences with a new antihistaminic drug, Jr. Allergy, 1946, xvii, 210.
8. Jenkins, D. E., Schreiber, E. O., and Sheldon, J. M.: Benadryl (b-dimethylaminoethyl benzhydryl ether HCl) in the treatment of hay fever and asthma, Univ. Hosp. Bull., Ann Arbor, 1946, xii, 30.
9. McGavack, T. H., Elias, H., and Boyd, L. J.: The influence of dimethylaminoethyl benzhydryl ether HCl (benadryl) upon normal persons and upon those suffering from disturbances of the autonomic nervous system. Preliminary report, Jr. Lab. and Clin. Med., 1946, xxxi, 560.
10. Barefoot, S. W., Riley, K. A., and Kuhn, B. H.: B-dimethylaminoethyl benzhydryl ether HCl in the treatment of urticaria and related dermatoses, N. Carolina Med. Jr., 1946, vii, 150.
11. Barnett, S. E., Barbas, F. M., and Goss, S. B.: Benadryl in hay fever, asthma and vasomotor rhinitis, Jr. Mich. Med. Soc., 1946, xlv, 771.
12. Zolov, B.: Benadryl—a new antihistamine agent in allergic disease, Jr. Maine Med. Assoc., 1946, xxxvii, 126.
13. Friedlander, A. S.: The use of a histamine antagonist, b-dimethyl-aminoethyl benzhydryl ether HCl in allergic disease, Am. Jr. Med. Sci., 1946, ccxii, 185.
14. Arnold, H. L.: Symptomatic control of urticaria and its equivalents by "benadryl," Proc. Clinic, Honolulu, 1945, xi, 123; Benadryl in chronic urticaria, Arch. Dermat. and Syph., 1946, liv, 71.
15. Lofstrom, J. E., and Nurnberger, E. E.: Irradiation sickness: histamine effect treated with benadryl, Am. Jr. Roentgenol., 1946, lvi, 211.
16. Schwartz, E., and Levin, L.: Benadryl in the symptomatic treatment of allergy, N. Y. State Jr. Med., 1946, xlvi, 1233.
17. Logan, G. B.: The use of benadryl in treating some of the allergic diseases of childhood, Proc. Staff Meet., Mayo Clin., 1945, xx, 436.
18. O'Leary, P. A., and Farber, E. M.: Evaluation of benadryl in the treatment of urticaria, scleroderma and allied disturbances, ibid., 1946, xxi, 295.
19. McGavack, T. H., Elias, H., and Boyd, L. J.: Some pharmacological and clinical experiences with dimethylaminoethyl benzhydryl ether HCl (benadryl), Bull. N. Y. Acad. Med., 1946, xxii, 481.
20. Notier, V. A., and Roth, G. M.: Treatment of hypersensitiveness to cold with benadryl: report of a case, Proc. Staff Meet., Mayo Clin., 1946, xxi, 170.
21. Taub, S. J.: The use of a new anti-histamine drug (benadryl) in allergic diseases, Quart., Chicago Med. School, 1945, vii, 6.
22. Harley, D.: Benadryl in hay fever, Lancet, 1946, ii, 158.
23. MacInnis, H. F.: Clinical observations on the use of benadryl, a new anti-histamine compound, Canad. Med. Assoc. Jr., 1946, lv, 476.
24. Friedlander, S.: Experimental and clinical evaluation of synthetic anti-histamine drugs, Am. Jr. Med., 1946, i, 174.
25. Kelly, W. H.: Anti-histamine agents, Jr. S. Carolina Med. Assoc., 1946, xlii, 209.
26. Todd, L. C.: Some clinical observations on the use of benadryl for the symptomatic relief of allergic conditions, Ann. Allergy, 1946, iv, 282; N. Carolina Med. Jr., 1946, vii, 308; Urticaria—with observations on the use of the new anti-histamine drug, benadryl, South. Med. and Surg., 1946, cviii, 1.
27. Friedlander, S., and Feinberg, S. M.: Histamine antagonists: III. The effect of oral and local use of b-dimethylaminoethyl benzhydryl ether hydrochloride on the whealing due to histamine, antigen-antibody reactions, and other whealing mechanisms; therapeutic results in allergic manifestations, Jr. Allergy, 1946, xvii, 129.

28. Williams, H. L.: Use of benadryl in the syndrome of physical allergy of the head: a preliminary report, Proc. Staff Meet., Mayo Clin., 1945, xx, 434.
29. Blank, W. H.: Some clinical experiences with benadryl, Jr. Med. Assoc. Alabama, 1946, xv, 367.
30. Bowen, R.: Benadryl, its therapeutic value in allergy, Texas State Jr. Med., 1946, xlii, 188.
31. Slater, B. J., and Francis, N.: Benadryl, a contributing cause of an accident, Jr. Am. Med. Assoc., 1946, cxxxii, 212.
32. Rieveschl, G., Jr., and Gruhzit, O. M.: A toxicologic study of histamine antagonist b-dimethylaminoethyl benzhydryl ether HCl (benadryl), Fed. Proc., 1945, iv, 150.
33. Loew, E. R., MacMillan, R., and Kaiser, M. E.: Anti-histamine properties of benadryl, b-dimethylaminoethyl benzhydryl ether hydrochloride, Jr. Pharmacol. and Exper. Therap., 1946, lxxxvi, 229.
34. Code, C. F.: A discussion of benadryl as an antihistaminic substance, Proc. Staff Meet., Mayo Clin., 1945, xx, 439.
35. Feinberg, S. M.: Histamine and antihistaminic agents, Jr. Am. Med. Assoc., 1946, cxxxii, 702.
36. Wells, J. A., Morris, H. C., Bull, H. B., and Dragstedt, C. A.: Observations on the nature of the antagonism of histamine by b-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl), Jr. Pharmacol. and Exper. Therap., 1945, lxxxv, 122.
37. Loew, E. R., Kaiser, M. E., and Moore, V.: Synthetic benzhydryl alkamine ethers effective in preventing fatal experimental asthma in guinea pigs exposed to atomized histamine, Jr. Pharmacol. and Exper. Therap., 1945, lxxxiii, 120.
38. State, D., and Wangensteen, O. H.: Procaine intravenously in the treatment of delayed serum sickness, Jr. Am. Med. Assoc., 1946, cxxx, 990.
39. Weil, H. R.: Unusual side effect from benadryl, ibid., 1947, cxxxiii, 393.
40. Schwartzberg, S., and Willerson, D.: Prolonged reaction to benadryl, ibid., 1947, cxxxiii, 393.
41. Borman, M. C.: Danger with benadryl of self medication and large dosage, ibid., 1947, cxxxiii, 394.
42. Geiger, J., Rosenfield, S. Z., and Hartman, D. L.: Unusual reaction following benadryl administration, ibid., 1947, cxxxiii, 392.

CHRONIC AURICULAR FLUTTER *

By Nathan M. Fenichel, M.D., F.A.C.P., *Brooklyn, N. Y.*

During the past three years, three cases of auricular flutter in which the arrhythmia has persisted for prolonged periods have been seen. This is an occurrence at some variance with the general belief that auricular flutter is of short duration, a few weeks at most, and that its circus movement soon changes to either auricular fibrillation or else ceases with the resumption of normal sinus rhythm.

In the first patient, auricular flutter is still present after three years despite several attempts at interruption of the circus movement. In the second patient, the flutter remained for 15 months until his death from a cerebral hemorrhage. In the third patient the auricular flutter, after resisting all drug therapy, spontaneously changed to auricular fibrillation after several months.

* Received for publication June 18, 1947.
From the Medical Divisions of the Jewish Hospital and the Kings County Hospital, Brooklyn, New York.

Occasional cases of permanent auricular flutter have been reported previously. As stated by White,[1] auricular flutter may be paroxysmal or permanent, usually lasting for hours or days, occasionally for weeks, but rarely for months or years. Sprague and White [2] in 1928 reported a case of auricular flutter of five years' duration. In their case the ventricular rate averaged 130 per minute, but at times it reached 260 per minute with release of the auricular-ventricular block. Lewis [3] in 1937 described a case of auricular flutter which lasted uninterruptedly for 24 years, and which maintained a ventricular rate of 140 per minute with 2 to 1 auricular-ventricular block. Kossman and Berger [4] in 1941 recorded a case of auricular flutter which endured 11 years. White [5] in 1944 mentioned an additional case of permanent auricular flutter of 15 years' duration.

Case Reports

Case 1. Mrs. M. Z., aged 38, was readmitted to the Medical Service of the Jewish Hospital on March 28, 1944 because of palpitation, epigastric distress, enlargement of the abdomen, and nausea due to sensitivity to digitalis. Physical examination disclosed cyanosis of the lips, orthopnea, moderate distention of the neck veins, and an irregular heart rate of 136 with a marked pulse deficit. The heart was found to be considerably enlarged both to the left and to the right. Systolic and diastolic murmurs were audible at the apex, and the pulmonic second sound was accentuated. There were some basal pulmonary râles, and the liver was tender and enlarged to 6 cm. below the costal margin. The diagnosis was moderate congestive heart failure, and rheumatic heart disease with mitral stenosis and insufficiency and possible tricuspid insufficiency.

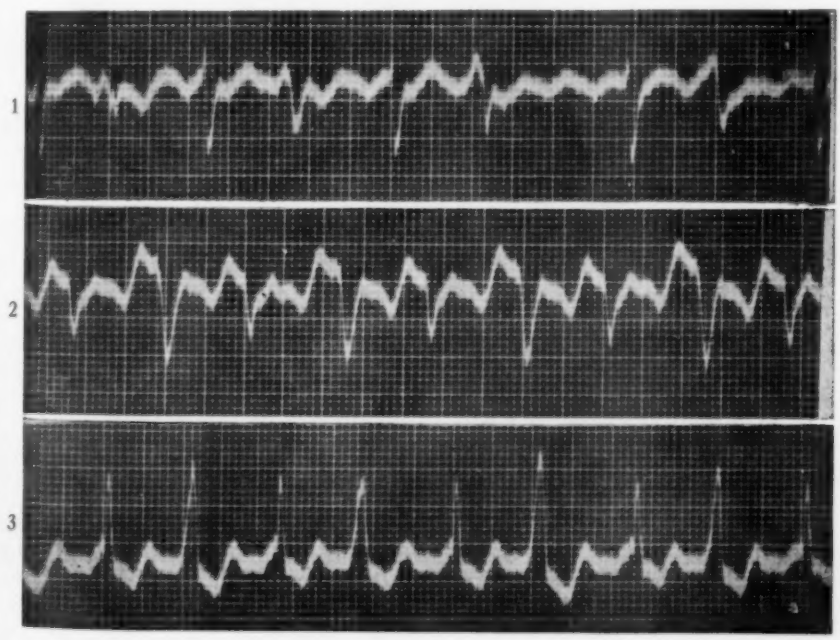

Fig. 1A. *Case 1,* April 3, 1944. Auricular flutter of 270 per min. The ventricular rate is about 130 and each alternate complex is a ventricular extrasystole producing bigeminal rhythm. The flutter waves are most conspicuous in Lead I where there is a temporary increase in the auriculoventricular block.

The arrhythmia was interpreted clinically as auricular fibrillation and additional digitalis was given on the day of admission. The following day distinct bigeminal rhythm was detected and the digitalis was withheld. On April 3, the electrocardiogram disclosed auricular flutter with a rate of 270, and a ventricular rate of 130 (figure 1A). Each second ventricular contraction was a ventricular extrasystole producing bigeminal rhythm in an otherwise 4 to 1 auricular-ventricular block. In Lead I, the flutter waves are clearly seen with a temporary increase in the block.

With only small doses of digitalis, the coupling disappeared within the next 10 days and the record of April 13 revealed auricular flutter of 240 with 4 to 1 block and a regular ventricular rate of 60. At this time rapid undulating pulsations of the cervical veins, due to the flutter, could easily be distinguished from the slow carotid pulsations.

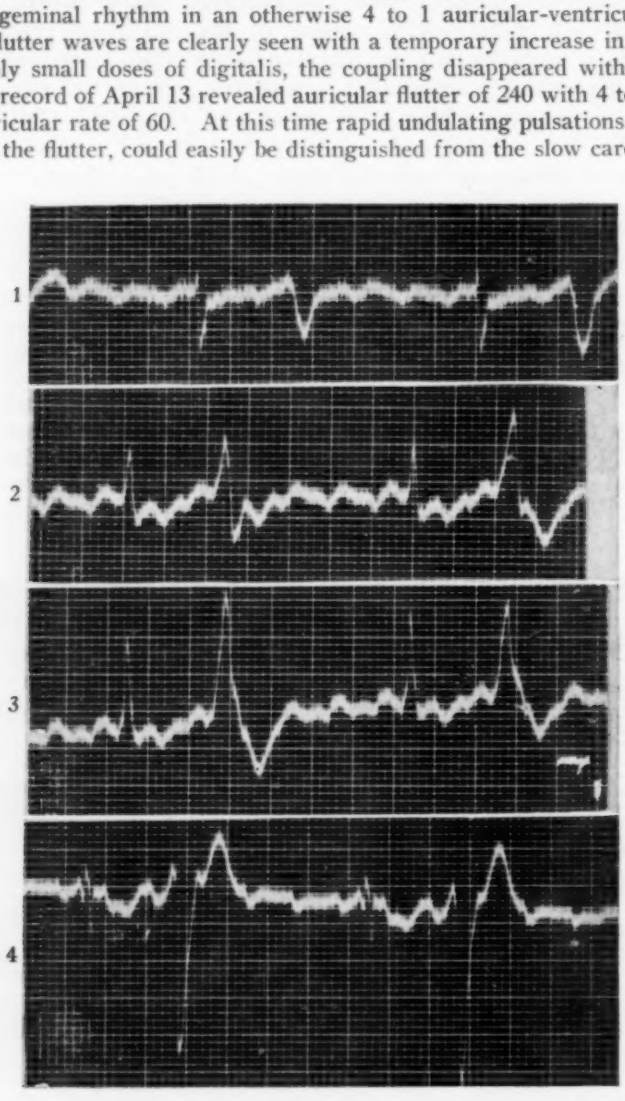

FIG. 1B. *Case 1*, July 27, 1944. Auricular flutter of 270. The ventricular rate is 90 and each alternate complex is a ventricular extrasystole producing bigeminal rhythm.

The patient maintained this status with half the usual maintenance dose of digitalis until her discharge, considerably improved, on May 3, 1944. She was given quinidine sulfate up to 0.8 gm. in eight hours, on several occasions, without altering the auricular circus movement. Larger doses of quinidine were not tolerated.

Since discharge from the hospital, she has been under observation for the past three years. She has been quite comfortable and able to perform light household duties. Her ventricular rate has been controlled with 0.1 mg. of digitoxin every two days, and she occasionally requires a mercurial diuretic. The auricular flutter, as confirmed by numerous electrocardiograms, persists and frequent episodes of bigeminal rhythm are also noted. Figure 1B taken July 27, 1944 shows auricular flutter with a rate of 270, and an average auriculoventricular block of 6 to 1. The normal ventricular rate is 45 and each of these complexes is followed by a ventricular extrasystole producing coupling. Figure 1C taken November 19, 1946 reveals an auricular flutter of 216 with 3 to 1 block and a regular ventricular rate of 72. The flutter waves are best seen in Leads I and IV. In Leads II and III, diphasic T-waves probably divide the flutter waves immediately following the QRS complexes.

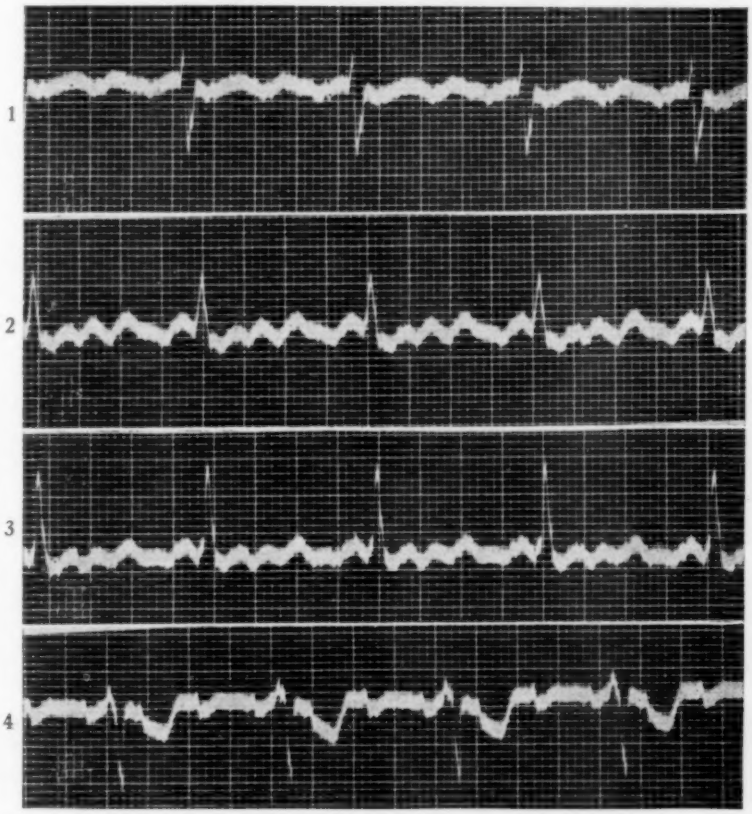

FIG. 1C. *Case 1*, Nov. 19, 1946. Auricular flutter of 216 with a constant 3 to 1 block and a ventricular rate of 72. The flutter waves immediately following the QRS complexes are split by diphasic T-waves in Leads II and III.

Case 2. Mr. B. W., aged 71, had been under observation since 1942 because of cerebral arteriosclerosis, moderate hypertension, and mild diabetes mellitus responding to a dietary regime. In June 1944 he experienced a sudden onset of precordial palpitation associated with a dry cough and increasing dyspnea. On examination on June 10 there was slight dyspnea and a few moist râles were heard at both bases. The heart rate was 145, regular except for an infrequent dropped beat. An electrocardio-

gram (figure 2A) disclosed auricular flutter with a rate of 290. The ventricular rate was about 145 with a predominant 2 to 1 auriculoventricular block and an occasional 3 to 1 ventricular response. The patient was digitalized within three days and quinidine sulfate 0.3 gm. t.i.d. was also prescribed. On June 16, the patient appeared much more comfortable and exhibited a regular heart rate of 75. However, on inspection in the supine position, the neck veins were seen to be undulating at an extremely rapid rate and persistence of the flutter was suspected. An electrocardiogram (figure 2B) now revealed an auricular flutter of 300 with a constant 4 to 1 auriculoventricular block.

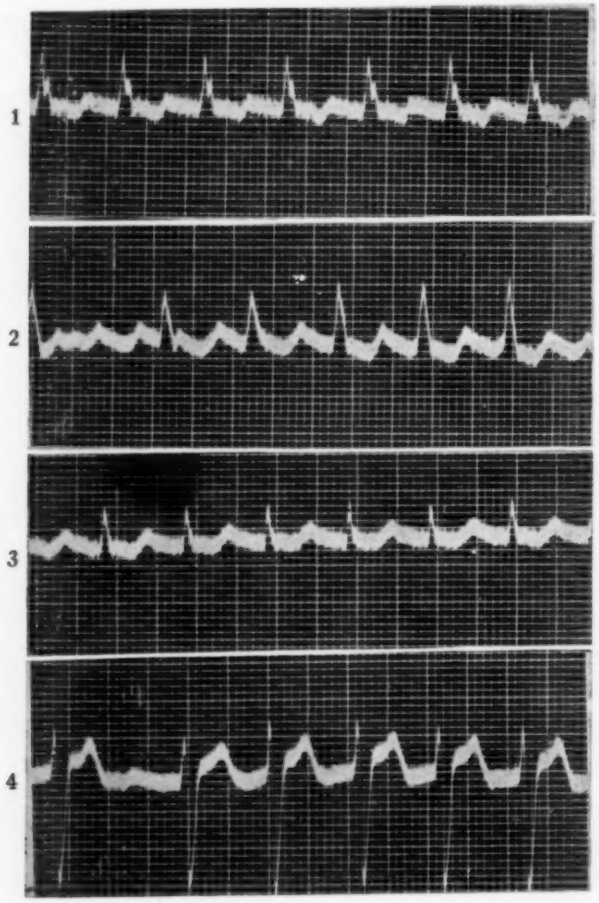

FIG. 2A. *Case 2,* June 10, 1944. Auricular flutter of 290 with a predominant 2 to 1 auriculoventricular block and a ventricular rate of about 145. The occasional 3 to 1 ventricular response is seen in Leads II and IV.

The patient was maintained on digitalis for the following 15 months, and on several occasions quinidine sulfate up to 2.0 gm. daily was administered without abolishing the auricular circus rhythm. He gradually developed congestive heart failure which responded to mercupurin injections. In May 1945, the electrocardiogram showed auricular flutter with a rate of 250, and an irregular ventricular rate of 80 due to a varying auriculoventricular block of 2 to 1, 3 to 1, and 4 to 1.

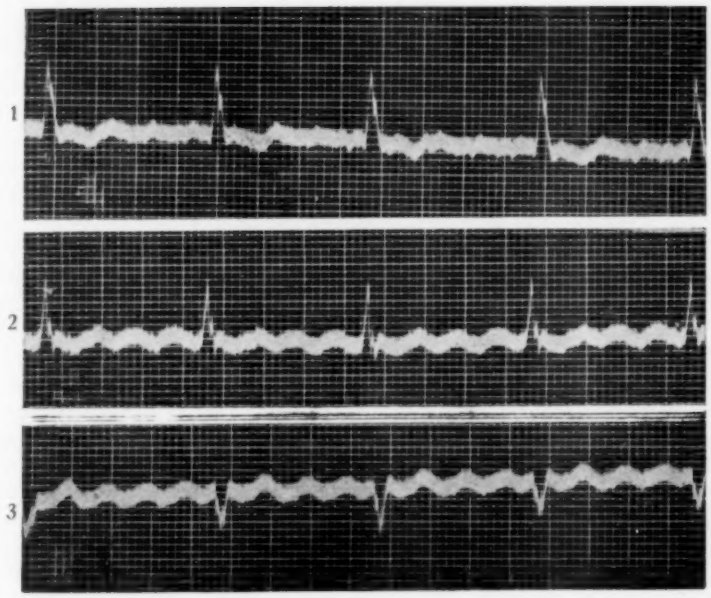

FIG. 2B. *Case 2,* June 16, 1944. Auricular flutter of 300 with a constant 4 to 1 auriculoventricular block.

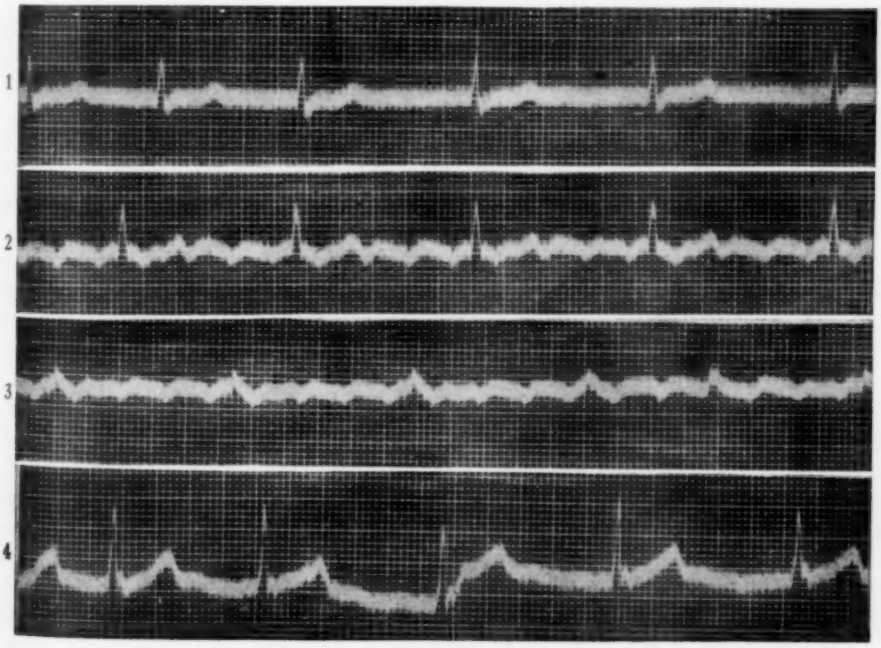

FIG. 3. *Case 3,* Aug. 10, 1946. Auricular flutter of 240 with a ventricular rate of 56. The auriculoventricular block varies from 3 to 1 to 5 to 1.

In September 1945 he lapsed into coma due to a cerebral hemorrhage and died within three days. The auricular flutter as revealed by the rapid pulsations of his cervical veins persisted until his death. Autopsy permission was denied.

Case 3. Mr. H. B., aged 77, was admitted to the medical service of the Kings County Hospital on August 9, 1946 because of pain and swelling of his right hand. He complained also of moderate palpitation experienced during the past few months. Examination disclosed an acute arthritis of the hand involving the wrist and interphalangeal joints. The cardiac rhythm was slightly irregular and the rate was about 60. His blood pressure was 210 mm. Hg systolic and 110 diastolic. Very rapid undulations of the cervical veins could be identified when the patient was lying flat in bed. The electrocardiogram of August 10 showed auricular flutter of 240 per minute with a ventricular rate of 56 and an auricular-ventricular block varying from 3 to 1 to 5 to 1 (figure 3).

In an endeavor to restore normal rhythm through the intermediate stage of auricular fibrillation, the patient was fully digitalized within three days. As observed in the daily electrocardiograms, the ventricular rate gradually decreased to 40 and the auriculoventricular block increased to as high as 9 to 1, but the flutter remained unaltered. Quinidine sulfate was then given in increasing doses up to 2.2 gm. within nine hours without any effect. However, on September 10, two days after the quinidine was discontinued and 10 days after all digitalis was withheld, the auricular rhythm spontaneously changed to fibrillation which persisted until his discharge, September 14. The arthritis of his hand gradually subsided with salicylate therapy.

As indicated by the history, the auricular flutter was probably present in this patient for several months prior to his admission and continued during one month of observation in the hospital.

Comment

Of these three patients with auricular flutter, the first patient suffered from rheumatic heart disease, and the other two from arteriosclerotic heart disease. Digitalis had no effect on the auricular arrhythmia in all three, but was required in the first two patients to increase the auriculoventricular block sufficiently to maintain a slow ventricular rate. The third patient exhibited a slow ventricular rate on admission, probably due to an organic block, and did not require maintenance doses of digitalis. Quinidine had no influence on the abnormal auricular rhythm of any of these patients.

Clinically in all three, the auricular flutter could be identified by rapid regular undulating pulsations of the cervical veins when the patient was supine and when the auriculoventricular block was greater than 2 to 1. With 2 to 1 block or less, the ventricular rate and hence the carotid pulsations were so rapid that their pulsations could not be differentiated from those of the veins.

The pulsations of the cervical veins in auricular flutter may sometimes be confused with unusually prominent a, c, and v jugular pulsations occurring with normal sinus rhythm when the venous pressure is high. In the latter instance, the pulsations are not regularly spaced and are of uneven amplitude throughout each cardiac cycle.

Summary

1. Chronic auricular flutter is not as rare as is generally believed. Three patients are presented in whom the abnormal rhythm lasted over three years, 15 months, and several months, respectively.

2. Chronic auricular flutter may be treated just as chronic auricular fibrillation with a sufficient maintenance dose of digitalis to slow the ventricular rate adequately.

BIBLIOGRAPHY

1. White, P. D.: Heart disease, 1944, The Macmillan Co., New York, p. 903.
2. Sprague, H. B., and White, P. D.: Auricular flutter. Report of a case of five years' duration with spontaneous restoration of normal rhythm, Jr. Am. Med. Assoc., 1928, xc, 1772.
3. Lewis, T.: Auricular flutter continuing for 24 years, British Med. Jr., 1937, i, 1248.
4. Kossman, C. E., and Berger, A. R.: Auricular flutter of eleven years' duration with observations on esophageal electrocardiograms, Ann. Int. Med., 1941, xv, 128.
5. White, P. D.: Heart disease, 1944, The Macmillan Co., New York, p. 906.

CODEINE ADDICTION *

By Charles M. Gruber, Ph.D., M.D., and Guy M. Nelson, M.D.,
Philadelphia, Pennsylvania

For approximately 100 years codeine has been used in therapeutics with total disregard of its possible addicting properties. Since it has a feeble euphoric action the addiction liability is not great. The first case of true addiction to codeine was reported by Pelz [1] in 1905. The drug which had originally been given to this patient in 30 mg. (½ grain) doses three times a day for "nervousness" was gradually increased to 1.5 gm. (22½ grains) orally per day and ultimately to 3 gm. (45 grains). Treatment of this patient by the method of abrupt and complete withdrawal was followed by a definite abstinence syndrome, indicating a physical dependence upon codeine. In 1913, Sollier [2] reported a patient who took the drug regularly for the relief of rheumatic pains and whose tolerance had increased until within three years a daily dosage of 2 gm. (30 grains) was reached. In this case, as in the case described above, withdrawal of the drug caused typical abstinence symptoms.

Himmelsbach and his associates [3] have collected from the literature the reports of 99 codeine addicts. Of these, 74 were reported as presumptive and 25 as definite addicts. Many of the presumptive addicts would probably have been placed in the definite class had more of the history been given in the reports.

Case Report

R. J. B., a white male, age 57, a physician, was admitted to Jefferson Hospital November 4, 1945, complaining of pain in the epigastrium which had persisted since 1937. His past history is relatively unimportant except that he had had the following known adult diseases and operations: Appendectomy, 1908; inguinal herniotomy, 1934; removal of left ureteral calculus, 1937; acute toxic hepatitis, 1937; chronic calculous cholecystitis, 1937; and cholecystectomy, 1938.

Physical examination showed an emaciated, well-developed male, in no apparent distress, but slightly lethargic. The breath had the odor of paraldehyde. Except

* Received for publication April 5, 1947.
From the Departments of Pharmacology and Medicine, Jefferson Medical College, Philadelphia, Pennsylvania.

for some tenderness and rigidity in the epigastrium, a liver edge palpable 3 cm. below the costal margin, and scars due to former operations, the physical examination was negative.

Roentgen-ray studies of the chest and of the gastrointestinal system revealed no unusual finding. The electrocardiogram was essentially normal. The liver function (bromsulfalein) test was within the normal range. The urine was essentially normal except that a test for urobilinogen was positive in dilutions of 1 to 20; however, only one such study was made. The urea clearance was 89 per cent. The stool was normal in the amount of bile pigment content. Except for low red blood cell count, low hemoglobin content, and some basophilic stippling of the red blood cells, nothing unusual was noted in the blood. On admission, the red blood cell count was 3,400,000 per cu. mm. and the hemoglobin level was 68 per cent; just before the patient left the hospital these had become 5,000,000 per cu. mm. and 91 per cent, respectively.

On questioning, the patient admitted that he had taken paraldehyde and ten 20 mg. (1/3 grain) tablets of "Pantopon" before entering the hospital, because of pain he had suffered due to the long trip from one of the Southern states to Philadelphia. He insisted that only on occasion did he use either morphine or "Pantopon" for the relief of pain, but admitted that he did use codeine freely and on occasion whiskey to excess. He had taken 0.66 gm. (10 grains) of codeine per day for several months, but became tolerant to this dose, and during the past several weeks, previous to coming to the hospital, he had been taking, hypodermically, 4.8 gm. (72 grains) of codeine sulfate daily. The discovery of the true state of affairs came about in the following way. Since the fact that the patient was suffering from codeine addiction was not realized and since he had taken, just before entering the hospital, large doses of "Pantopon" and paraldehyde, the dose of codeine given the first day was relatively small (table 1).

TABLE I

Summary of Treatment Used and the Average Heart Rate of the Patient during the Withdrawal of Codeine

Days of treatment	Control	1	2	3	4	5	6	7	8	9	10	11	12
Codeine sulfate in gm./24 hrs.	4.8	0.75	2.87	2.25	2.2	1.67	1.42	1.3	1.3	0.92	0.55	0.42	0.1
Demerol in mg./24 hrs.	0	0	0	400	500	600	500	600	500	500	500	500	0
Average heart rate	80	84	60	52	61	73	71	72	72	70	71	71	71

However, after the patient demanded 0.52 gm. (8 grains) of codeine one hour after having received 0.26 gm. (4 grains), the fact of his addiction was established; thereafter, the treatment for codeine addiction was relatively simple. In the following 24 hours he was given hypodermically 2.86 gm. (44 grains) of codeine sulfate in 0.26 gm. (4 grains) doses, as needed. This dose was gradually reduced until on the thirteenth day he received no codeine. Because of pain, of which he complained bitterly in the beginning of treatment, "Demerol" was started on the third day. This was given in 100 mg. doses hypodermically four to six times per day (table 1), and discontinued on the eleventh day. On the twelfth to the fifteenth days, inclusive, he was given hypodermic injections of sterile distilled water.

The withdrawal symptoms were marked and definite. He complained of increased pain in the abdomen, muscular weakness, leg cramps, and muscular twitching. He became restless, nervous, jittery, and was unable to sleep. Whether this was due

to the pain or due to the withdrawal of codeine cannot be stated conclusively; however, from the ninth day on, with a marked reduction in codeine intake, the patient slept well, complained of no pain, was talkative and stated that he felt fine. He continued to sleep well, remained pleasant and suffered no pain during the remainder of his stay in the hospital even though he received only acetylsalicylic acid, as needed, and injections of sterile distilled water. During the first three days of drug restriction the respiration rate deceased from 20 to as low as 12 per minute, the temperature dropped from 98.6° to 97.9° F., and the pulse rate from 80 to as low as 52 beats per minute with a corresponding insignificant fall in both systolic and diastolic blood pressures.

During the first eight days of treatment he lost 15 pounds in weight, which he slowly regained during his stay in the hospital. Several days after complete withdrawal of codeine he was informed of his addiction problem. While in the hospital he continued relatively symptom free; after leaving the hospital he went to his home, arranged his personal affairs, and then took his own life.

Summary

The above patient, we believe, had a case of true codeine addiction. Tolerance had been acquired over a period of years and, upon withdrawal of the drug, abstinence symptoms occurred similar to those noted after the withdrawal of morphine.

BIBLIOGRAPHY

1. Pelz: Ein Beitrag zum Codeinesmus, Med. Wchnschr., 1905, xxxi, 864.
2. Sollier, P.: Un cas de codeinomanie pure, Rev. de med. leg. et de jurisprud. med., 1913, xx, 359.
3. Himmelsbach, C. K.: Studies on codeine addiction, U. S. Pub. Health Rep. Supplement, 1940, No. 158, 2.

EDITORIAL

Q FEVER

In 1935 the outbreak of an unknown fever among a large number of workers in a meat work in Brisbane, Australia, led Dr. E. H. Derrick, the Director of the Laboratory Section of the Queensland Health Department, to investigate the cause of the outbreak. These investigations, which lasted over several years, led to our first knowledge of what is now known as the clinical entity of "Q fever." In his first publication in 1937, Derrick [1] gave a thorough clinical description of nine typical cases of the infection and in addition reported his work on the nature of the virus causing the disease. He showed that guinea pigs are susceptible to Q fever; that they may be infected by inoculations of blood or urine from patients during the active stages of the disease and that after having recovered from their infection, the guinea pigs remained immune for many months to further inoculations. Guinea pigs killed during the active stage of their infection show on autopsy enlargement of the spleen and liver, and emulsions of both of these organs are highly infective to new guinea pigs. In the same year Burnet and Freeman [2] in Melbourne reported on further studies of the virus which had been isolated from Q fever patients by Derrick. They found that mice inoculated intraperitoneally with infected guinea pig liver showed enlargement of the spleen and liver with characteristic histological changes. In sections and smears of such infected mouse liver and spleen large numbers of rickettsial organisms were visible. These basic studies of Derrick and of Burnet and Freeman established the entity which is now widely known as Q fever.

In view of our more recent knowledge concerning the clinical course of Q fever, it is interesting to review the descriptions of the course of this disease given by Derrick, based on the nine patients included in his report. The onset of the illness in all cases was acute; first complaints were usually headache, pains in the back and limbs and fever. Four patients noted mild chilliness, two patients had a definite rigor. Fever in these cases was of very variable duration. In a milder type it lasted for approximately nine days. In other cases, however, the course was more prolonged, lasting from 14 to as much as 24 days. In only one of the nine patients was there a rash and this was of a not very specific character and did not appear until the fourteenth day of the illness. The white blood cell count was found within normal limits. In only two of these cases was cough mentioned as a symptom. However, in his discussion of the differential diagnosis of the disease, Derrick mentions that in some of the cases of Q fever, mild respiratory symptoms were present and that these patients were naturally regarded

[1] Derrick, E. H.: "Q" fever, a new fever entity: clinical features, diagnosis, and laboratory investigation, Med. Jr. Australia, 1937, ii, 281–299.

[2] Burnet, F. M., and Freeman, M.: Experimental studies of the virus of "Q" fever, Med. Jr. Australia, 1937, ii, 299–305.

at first as suffering from influenza until the continuance of the fever excluded this diagnosis.

After the discovery of the rickettsial nature of the infection, Derrick, Burnet and Freeman suspected that because of the absence of rash and the failure to agglutinate any of the proteus strains, as well as on differential points in the morphology of the Rickettsia that had been demonstrated, it was probable that Q fever represented a new rickettsial disease which could not readily be classified in existing groups of rickettsial infections.

In 1938 Gordon E. Davis and Harold R. Cox [3] reported upon the recovery of a filter passing infectious agent from ticks of the species *Dermacentor andersoni* which had been collected near Nine Mile Creek, about 32 miles west of Missoula, Montana. Parker and Davis [4] demonstrated that this infectious agent could be transmitted to guinea pigs through the *Dermacentor andersoni* acting as a vector. Cox [5] in a later report in the same year described the infectious agent as a gram negative pleomorphic rickettsia-like organism, that occurred both intra- and extra-cellularly in the affected tissues of the guinea pigs.

In describing an infection in a laboratory worker who had been exposed to the virus derived from ticks, Dyer [6] was able to show that the serum of this individual had protective properties against infection in animals with the Q fever strain of rickettsia, and that in addition, guinea pigs infected with this patient's blood upon recovery were found immune likewise to the fever of the tick virus. He suggested the probability that these two rickettsial diseases were identical. Meanwhile, the name *Rickettsia burneti* [7] had been proposed for the agent causing the Australian infection, and the name *Rickettsia diaporica* [8] had been suggested for the causative organism in the American infection.

Exchange of infective material from these two infections between the National Institute of Health and the Walter and Eliza Hall Institute in Melbourne led to studies which conclusively proved that the two infective organisms were identical.[9] Because of the priority of Burnet's isolation of the rickettsia, the organism is now universally known as *Rickettsia burneti.*

[3] DAVIS, G. E., and COX, H.: A filter-passing infectious agent isolated from ticks. I. Isolation from *Dermacentor andersoni,* reaction in animals and filtration experiments, Pub. Health Rep., 1938, liii, 2259–2267.

[4] PARKER, R. R., and DAVIS, I. E.: A filter-passing infectious agent isolated from ticks. II. Transmission by *Dermacentor andersoni,* Pub. Health Rep., 1938, liii, 2267–2270.

[5] COX, H. R.: A filter-passing infectious agent isolated from ticks. III. Description of organism and cultivation experiments, Pub. Health Rep., 1938, liii, 2270–2276.

[6] DYER, R. E.: A filter-passing infectious agent isolated from ticks. IV. Human infection, Pub. Health Rep., 1938, liii, 2277–2284.

[7] DERRICK, E. H.: *Rickettsia burneti:* the cause of Q fever, Med. Jr. Australia, 1939, i, 14.

[8] COX, H. R.: Studies of a filter-passing infectious agent isolated from ticks. V. Further attempts to cultivate in cell-free media. Suggested classification, Pub. Health Rep., 1939, liv, 1822–1827.

[9] BURNETT, F. M., and FREEMAN, M.: A comparative study of Rickettsiae strains from an infection of ticks in Montana (United States of America) and from "Q" fever, Med. Jr. Australia, 1939, ii, 887–891.

Infections of laboratory personnel with the *Rickettsia burneti* have been a striking feature of the development of our knowledge concerning this organism. Such infections occurred in Derrick's Laboratory in Brisbane [10] and in the laboratory of Burnet in Melbourne.[11] As has already been mentioned the infection of a laboratory worker with the virus of the American strain of *Rickettsia burneti* led to the experiments by Dyer [6] which suggested the identity of this American infection with that which had been reported in Australia.

A further advance in our knowledge of the clinical course of the disease in man arose from a study of 15 cases of Q fever which developed in one building of the National Institute of Health in Washington in the spring of 1940. Hornibrook [12] entitled his report on this outbreak as "An Institutional Outbreak of Pneumonitis." Apparently the clinical symptoms in these patients were very similar to those reported originally by Derrick. The onset in all the cases was sudden, often with chilly sensations and general malaise. Headache of a severe and persistent character was an outstanding symptom. Chills and sweats were not uncommon. A few patients developed a short, hacking cough, but in none was it productive of a rusty sputum and aside from vague neuralgic-like chest pains, there were no other symptoms to indicate pulmonary involvement, nor were distinctive physical signs present on examination of the lungs. Nevertheless, roentgen-ray examination of the chest gave consistent evidence of pulmonary lesions. Soft infiltrative types of lesions, sometimes single but often multiple, were seen in the films. The densities were described as being of a more patchy type than is observed in the usual bronchopneumonia and less uniform in density than the shadows derived from lobar pneumonic involvement. Sputum examination showed no typical pneumococci. Mice injected with sputum were negative for the pneumococcus; and sulfapyridine did not exert any specific effect upon the pulmonary lesions nor upon the course of the disease. The disease in these cases was of varying severity, but in one instance proved fatal. Dyer, Topping and Bengtson [13] studied the outbreak from the point of view of the causative agent and were able to report upon the demonstration of *Rickettsia burneti* in three out of four cases in which procedures to effect this isolation were carried out. These authors pointed out the similarity of the clinical course and of the roentgenological findings in these cases with the descriptions of a non-pneumococcic pulmonary infection which had been described in the United States during the years 1935 to 1940 by various authors under the names of "atypical pneumonia," "pneu-

[10] SMITH, D. J. W., BROWN, H. E., and DERRICK, E. H.: A further series of laboratory infections with the Rickettsia of "Q" fever, Med. Jr. Australia, 1939, i, 13–14.

[11] BURNET, F. M., and FREEMAN, M.: Note on a series of laboratory infections with the Rickettsia of "Q" fever, Med. Jr. Australia, 1939, i, 11–12.

[12] HORNIBROOK, J. W., and NELSON, K. R.: An institutional outbreak of pneumonitis. I. Epidemiological and clinical studies, Pub. Health Rep., 1940, lv, 1936–1944.

[13] DYER, R. E., TOPPING, N. H., and BENGTSON, I. A.: An institutional outbreak of pneumonitis. I. Isolation and identification of causative agent, Pub. Health Rep., 1940, lv, 1945–1954.

monitis," "broncho-pneumonia of unknown etiology," etc. The discovery of inapparent pneumonitis as a characteristic feature of Q fever in man marks the opening of a new era in the recognition of this disease entity.

Though the infections in laboratory workers cited above added to the clinical picture of the disease in man, they did nothing to elucidate the mode of transmission of this infection to the human. In the case of the outbreak in the laboratory of Burnet in Melbourne, ecto-parasites of the laboratory mice were suspected as vectors but no conclusive proof was adduced. Similarly, a careful epidemiological study of the infection in the personnel in the National Institute of Health did not throw any light on the mode of their infection. However, Derrick, Smith, Brown and Freeman had carried on investigations as to the occurrence of the disease in animals in their natural state and in 1939 published a report [14] in which they demonstrated that the bandicoot, *Isoodon torosus,* "a common, small animal in the Australian bush," was susceptible to the disease when inoculated with infective material, and moreover, that of 44 bandicoots tested before inoculation, four were shown to possess immune bodies to the virus of Q fever in the form of serum agglutinins against the *Rickettsia burneti.*

Having obtained evidence that the disease occurred in bandicoots in nature, it was a natural next step for the Australian investigators to search for a tick vector. Smith and Derrick [15] in 1939 reported the isolation of six strains of *Rickettsia burneti* from the tick *Haemaphysalis humerosa.* This tick is one of the common ecto-parasites of the bandicoot. The ticks were collected from bandicoots on Moreton Island, ground up in a mortar and the emulsion injected intraperitoneally into guinea pigs. Infection of the guinea pigs occurred. The homology of the tick-strains with strains of human origin was confirmed by their characteristic behavior during animal passage. The strains obtained in guinea pigs were transferred to mice in which typical rickettsia were demonstrated. The authors noted that the *Haemaphysalis humerosa* had been reported as occurring in a variety of host animals along the eastern and northern seaboards of Australia. There was record of its having been found on cattle. The authors were able to show that though *H. humerosa* had not previously been observed to attack man, they were able to induce it to feed on man under experimental conditions in the laboratory. They point out, however, that the significance of this naturally infected tick in the epidemiology of Q fever is not clear since a history of tick bite is not a feature of the human infection. A further paper by Derrick and Smith [16] in 1940 reported the isolation of three strains of *Rickettsia burneti* from the bandicoot, thus establishing definitely the occurrence in nature of a host ani-

[14] Derrick, E. H., Smith, D. J. W., and Brown, H. E.: The role of the bandicoot in the epidemiology of "Q" fever: a preliminary study, Med. Jr. Australia, 1939, i, 150–155.

[15] Smith, D. J. W., and Derrick, E. H.: Studies in the epidemiology of "Q" fever. I. The isolation of six strains of *Rickettsia burneti* from the tick *Haemaphysalis humerosa,* Australian Jr. Exper. Biol. and Med. Sci., 1940, xviii, 1–8.

[16] Derrick, E. H., and Smith, D. J. W.: Studies in the epidemiology of "Q" fever. II. The isolation of three strains of *Rickettsia burneti* from the bandicoot *Isoodon torosus,* Australian Jr. Exper. Biol. and Med. Sci., 1940, xviii, 99–102.

mal and a vector arthropod parasite. Further work reported by Smith [17] indicated that larval, nymphal and adult stages of the tick could be infected with rickettsia by feeding them upon infected guinea pigs during the febrile period. Smith showed, moreover, that the feces of infected ticks were highly infectious, being capable of infecting guinea pigs when applied either to abraded or unabraded skin.

Utilizing as an indication of infection the presence in serum of agglutinins for an emulsion of *Rickettsia burneti,* epidemiological surveys [18] were conducted. The first human survey was made at the Brisbane abattoir, where the original cases of Q fever had been discovered. Of 79 sera tested, 18 were found to show agglutination. Of these 12 had either had an attack of Q fever previously or a suspicious febrile illness not so diagnosed. In six instances, however, the individuals concerned were not aware of having had any fever. Similar positive agglutination tests were found in other workers and led the authors to the conclusion that Q fever may occur as an inapparent infection in the human.

An interesting observation was recorded in connection with the testing of cattle sera on a dairy farm, the owner of which had had Q fever himself six months previously. One of the 24 cow sera tested was completely positive.

The surveys on bandicoot sera showed a very high percentage of infected animals on Moreton Island. This was of interest in that 180 militia who encamped for training on this island did not in a single instance develop at a later date agglutinins for *Rickettsia burneti.* This result was taken to indicate that the tick *H. humerosa,* the common ecto-parasite of the bandicoots on Moreton Island, does not readily attack man and probably is not a common cause of direct human infection. The Australian group [19] of investigators tested nine species of bush animals apart from the bandicoot for susceptibility to Q fever and found that seven rodents and two marsupials were all susceptible upon inoculation. The failure to establish connection between the infected bandicoots and their infected ecto-parasites and human infections naturally led to renewed attention to other possible modes of transmission of the disease. The study [20] of the occupation and geographical distribution of Q fever patients in Australia showed that nearly all patients who lived in the country were associated with cattle and that practically all of the city patients in Brisbane worked at the meat works. In 1942 Derrick, Smith and Brown [20] demonstrated that calves were susceptible to inoculations with

[17] SMITH, D. J. W.: Studies in the epidemiology of "Q" fever by the tick *Haemaphysalis humerosa,* Australian Jr. Exper. Biol. and Med. Sci., 1940, xviii, 103–118.

[18] FREEMAN, M.: Studies in the epidemiology of "Q" fever. V. Surveys of human and animal sera for *Rickettsia burneti* agglutinins, Australian Jr. Exper. Biol. and Med. Sci., 1940, xviii, 193–200.

[19] DERRICK, E. H., SMITH, D. J. W., and BROWN, H. E.: Studies in the epidemiology of Q fever. VI. The susceptibility of various animals, Australian Jr. Exper. Biol. and Med. Sci., 1940, xviii, 409–413.

[20] DERRICK, E. H., SMITH, D. J. W., and BROWN, H. E.: Studies in the epidemiology of Q fever. IX. The role of the cow in the transmission of human infection, Australian Jr. Exper. Biol. and Med. Sci., 1942, xx, 105–110.

Q fever virus, and that after a brief illness so induced, the virus could be again isolated from the tissues. Cattle ticks were fed on one of the calves and some of these ticks became infected as demonstrated by guinea pig inoculation. The feces from such ticks contained *Rickettsia burneti*. Agglutinins for the *Rickettsia burneti* were found in the sera of 12 out of 879 dairy cattle in the Q fever endemic area. The authors concluded that it was likely that the cow becomes infected from the animal reservoir by means of ticks and that they can then transmit the infection to humans either directly from their tissues or indirectly from the crushed tissues or feces of their tick.

In the United States during the period of the above cited epidemiological investigations in Australia, work was proceeding on methods of growing the *Rickettsia burneti*. From the infected yolk sacs of developing chick-eggs abundant rickettsial material was obtained.[21] An adequate complement-fixation technic was developed for the serological separation of the rickettsial agents of endemic typhus, Q fever and Rocky Mountain Spotted Fever.[22] Complement fixation has proved a highly useful diagnostic tool in the later investigations on outbreaks of Q fever in different parts of the world.

Prior to entry of America into World War II, interest in Q fever was confined largely to those particularly concerned with investigations into the various forms of rickettsial disease. Developments during the war and after, however, have shown that this entity has a wider significance to the internist and general practitioner. During the winter and spring of 1944 to 1945 there occurred eight outbreaks of a febrile disease which closely resembled primary atypical pneumonia among allied troops in Italy, Greece and Corsica.[23, 24] Certain clinical, epidemiological and laboratory features were noted in these outbreaks which led to a more active investigation of the etiologic agent concerned. In three of the outbreaks animal inoculations led to the recovery of a rickettsial organism which was eventually shown to be identical with *Rickettsia burneti*. In five further outbreaks satisfactory serum samples obtained from patients showed specific antibody against this rickettsial agent. In May and June of 1945 an outbreak occurred among troops in transit from southern Italy to Camp Patrick Henry, Virginia and other ports of debarkation in the United States.[25] A study of the cases occurring at Camp Patrick Henry by immunological methods showed that the disease in question was Q fever. Evidence was obtained that the Ger-

[21] Cox, H. R.: The cultivation of *Rickettsia diaporica* in tissue culture and in the tissue of developing chick embryos, Pub. Health Rep., 1939, liv, 2171–2177.

[22] Plotz, H.: Complement-fixation in rickettsial diseases, Science, 1943, xcvii, 20–21.

[23] Robbins, F. E., and Ragan, C. A.: Q fever in the Mediterranean area: report of its occurrence in allied troops. I. Clinical features of the disease, Am. Jr. Hyg., 1946, xliv, 6–22.

[24] Robbins, F. E., Gauld, R. L., and Warner, F. B.: Q fever in the Mediterranean area: report of its occurrence in allied troops. II. Epidemiology, Am. Jr. Hyg., 1946, xliv, 23–50.

[25] Feinstein, M., Yesner, R., and Marks, J. L.: Epidemics of Q fever among troops returning from Italy in the spring of 1945. I. Clinical aspects of the epidemic at Camp Patrick Henry, Virginia, Am. Jr. Hyg., 1946, xliv, 72–87.

man troops in Greece had suffered with a clinically similar infection.[26] Dr. J. Caminopetros of the Pasteur Institute of Greece had isolated the strain in guinea pigs. When carried to the United States for study this strain was propagated in chick embryos and shown to contain rickettsiae similar to those of Q fever.

The epidemiological studies made in these outbreaks which involved many hundreds of cases did not add to the sum of knowledge concerning the mode of transmission of the infection to man. No natural hosts of the diseases were identified in the areas concerned, nor were any infected vectors discovered. It was shown that the outbreaks were often explosive in nature with a high attack rate among the bodies of troops concerned. It was concluded as a result of serological studies among the natives of the regions in which the troops were quartered that the disease was probably endemic in these areas. As noted by previous observers the presence of immune bodies in the sera of men who had not suffered from apparent infection indicated that mild and clinically asymptomatic cases probably occurred.

The clinical differentiation of Q fever from primary atypical pneumonia of unknown etiology was suggested by the marked lack of respiratory symptoms in Q fever, in spite of the presence of roentgenologically detectable areas of consolidation in the lungs; and likewise by the absence in Q fever of cold agglutinins which had been shown to be present in over 90 per cent of the cases of primary atypical pneumonia of unknown etiology. A high degree of infectiousness of the rickettsial agent was again demonstrated by an outbreak of 20 cases in the 15th Medical General Laboratory in which studies on the disease were being carried forward.[27] Further details concerning the roentgenological evidences of lung consolidation were obtained from the study of this large human material.[28] It was shown that the chest film taken on admission to the hospital was often clear, consolidation appearing for the first time on the third, fourth or in some cases as late as the sixth day of the disease. The patchy area of consolidation which then appeared was more commonly found in the lower than in the upper lobe. In some instances several lesions were present. The density was of a homogeneous ground-glass appearance. It was often very slow in resolution. Of 33 patients followed for an average of 22 days, only six had negative lung findings on roentgen-ray at the time of discharge from the hospital.

Shortly after the close of the war a serious outbreak of Q fever occurred again in the National Institute of Health.[28] Forty-seven cases were involved. In each instance the person had a history of having been in one building of the National Institute of Health within 24 days before the onset

[26] Robbins, F. C., Ragain, C. A., Gauld, R. L., Rustigian, R. et al: Q fever: a foreword. Introduction to a series of papers dealing with Q fever, Am. Jr. Hyg., 1946, xliv, 1–5.

[27] Robbins, F. E., and Rustigian, R.: Q fever in the Mediterranean area: report of its occurrence in allied troops. IV. A laboratory outbreak, Am. Jr. Hyg., 1946, xliv, 64–71.

[28] Huebner, R. J.: Report of an outbreak of Q fever at the National Institute of Health. II. Epidemiological features, Am. Jr. Pub. Health, 1947, xxxvii, 431–440.

of illness. In this building the Rickettsial Disease Unit of the Institute was located. In the same period as the human outbreak there occurred an outbreak of the disease in two guinea pig colonies in the same building. Huebner in reporting upon the epidemiological features of this outbreak drew attention to the unusual degree of resistance of the *Rickettsia burneti* to heat and to formalin. He also showed that there was a correlation between the dates of preparation in the Institute of yolk sac antigens and the probable dates of exposure in the human cases.

The first explosive outbreak of an acute febrile illness in the civilian population of the United States identified as Q fever occurred during the month of March in 1946 in Amarillo, Texas.[29] It appeared among the employees of a stockyard, a live-stock auction company and a nearby meat-packing plant. Among the total of 136 employees of these three establishments, there were 55 cases of Q fever with two deaths, an attack rate of 40 per cent. The clinical symptoms[30] in these cases were essentially the same as those described in the European epidemics and in the original cases in Australia. Roentgenographic evidence of pulmonary consolidation was obtained in the majority of hospitalized cases. Diagnosis by means of complement-fixation reaction indicated that the infection had occurred without clinical symptoms in some of the personnel.[31] From the serum of two cases in this epidemic *Rickettsia burneti* were isolated and identified.[32]

In August of 1946 another outbreak in a packing house in Chicago occurred with 30 cases affected.[33] In neither of these outbreaks was the epidemiological evidence obtained sufficient to indicate conclusively the mode of transmission of infection to the individual who came down with the disease. While in the majority of instances close contact with cattle and with their blood and organs in the killing rooms had been experienced there were other cases in which the degree of contact was quite remote.

In the preceding account of the development of our knowledge of Q fever prior to 1947, it will have been noted that the disease in human beings has occurred in the form of outbreaks in meat packing plants, in laboratories working with the disease and in units of military personnel. In addition, however, mention has been made of sporadic cases occurring in the coastal area of northeastern Australia, in Greece and in Italy. It might be added

[29] TOPPING, N. H., SHEPARD, C. C., and IRONS, J. V.: Q fever in the United States. I. Epidemiological studies of an outbreak among stock handlers and slaughterhouse workers, Jr. Am. Med. Assoc., 1947, cxxxiii, 813–815.

[30] IRONS, J. V., and HOOPER, J. M.: Q fever in the United States. II. Clinical data on an outbreak among stock handlers and slaughterhouse workers, Jr. Am. Med. Assoc., 1947, cxxxiii, 815–818.

[31] IRONS, J. V., MURPHY, J. N., and WOLFE, D. M.: Q fever in the United States. III. Serologic observations in an outbreak among stock handlers and slaughterhouse workers, Jr. Am. Med. Assoc., 1947, cxxxiii, 818–820.

[32] COX, H. R., TESAR, W. C., and IRONS, J. V.: Q fever in the United States. IV. Isolation and identification of Rickettsia in an outbreak among stock handlers and slaughterhouse workers, Jr. Am. Med. Assoc., 1947, cxxxiii, 820–821.

[33] SHEPARD, C. C.: An outbreak of Q fever in a Chicago packing house, Am. Jr. Hyg., 1947, xlvi, 185–192.

that such sporadic cases have likewise been observed in Panama, Switzerland and in Germany.

In the United States, however, prior to 1947 no true endemic area of Q fever had been detected. Since the spring of 1947, however, well over 150 cases have been detected and serologically proven in southern California, in an area including Los Angeles, Ventura, Santa Barbara and Orange Counties.[34, 35] Intensive work on the disease has been in progress in this area in the Q Fever Laboratory which was established in September, 1947 as a coöperative undertaking of the National Institute of Health, the California State Department of Public Health and the Los Angeles County Health Department. It has been found that proximity to dairies by reason of occupation or residence was a common factor in the histories of a large percentage of these cases. This led to intensive study of the cow as a factor in the transmission of the disease. A serological survey of over 2000 cows in Los Angeles County disclosed that approximately 13 per cent possessed serum antibodies against Q fever. It is of interest that less than 2 per cent of calves and bulls tested yielded serum reaction indicative of Q fever. Demonstrable illness in the reacting animals was absent. It proved impossible to recover the rickettsia of Q fever from the blood, the urine or the feces of the infected cows. On the other hand, when raw milk from the cows was tested, positive results in a high proportion of cases were at once obtained. These rickettsia were identified as identical with the *Rickettsia burneti* by morphological and all immunological reactions. It was found that pasteurization by acceptable methods sterilized the rickettsia-infected milk. This significant discovery has, however, not solved the problem of transmission of the disease from the cow to the human. The epidemiological investigations have clearly indicated that in a major proportion of the human cases the drinking of raw milk could not be incriminated as the cause of the transmission of the disease. It is evident, however, that inapparent infections of Q fever in cows are probably of great importance in the infection chain of Q fever.

It is believed by many that the widespread surveys now in progress in which there is being employed an antigen for complement-fixation studies which is more sensitive than that employed in earlier years, will result in the discovery of other endemic foci of Q fever in the United States. The disease is of growing importance to the practicing physician. It should be considered along with influenza, pulmonary tularemia, psittacosis, coccidioidomycosis, histoplasmosis and primary atypical pneumonia in determining the diagnosis in that puzzling group of patients who in addition to fever and malaise show a pulmonic consolidation for which no bacterial organism can be incriminated as the etiologic agent.

M. C. P.

[34] Huebner, R. J., Jellison, W. L., Beck, M. D., Parker, R. R., and Shepard, C. C.: Q fever studies in southern California, Pub. Health Rep., 1948, lxiii, 214.

[35] Meyer, H. F.: The animal kingdom, a reservoir of human disease, Ann. Int. Med. In press.

REVIEWS

Essentials of Endocrinology. 2nd Ed. By ARTHUR GROLLMAN, Ph.D., M.D., F.A.C.P. 644 pages; 16 × 24 cm. J. B. Lippincott Company, Philadelphia. 1947. Price, $10.00.

This is the second edition of a book which first appeared in 1941. In the preface, the author states that he has attempted to develop the subject on the basis of scientific background rather than on purely clinical concepts.

Endocrinology is a field which has developed rapidly and which is intimately related to a number of diseases which are fundamentally non-endocrine. Accordingly, it is difficult in a book of this size adequately to present the numerous ramifications of aberrations in function of the various glands.

The endocrine glands are considered from the standpoint of their structure, their function and the various clinical disorders which derive from altered physiology. The author advocates the use of anterior pituitary extracts in treating panhypopituitarism, the unitarian theory of adrenal cortical hormones, iodine therapy for simple goiter. These and other statements will be questioned by many.

The references are adequate, the illustrations are helpful and the format of the book is excellent.

J. Z. B.

The Peripheral Circulation in Health and Disease: A Study in Clinical Science. By ROBERT L. RICHARDS, M.D., Rockefeller Fellow in Medicine; Formerly Assistant Physician, Neurovascular Unit, Gogarburn Hospital, Edinburgh. 153 pages; 17 × 27 cm. The Williams and Wilkins Company, Baltimore, Maryland. 1946. Price, $6.00.

This monograph presents an excellent review of the physiology of the peripheral circulation, particularly with reference to its interrelationship with the autonomic nervous system. Various pathologic entities are discussed, in addition to diagnostic measures.

The chapters on Peripheral Nerve Injuries and Immersion Foot Syndrome are particularly comprehensive and noteworthy, representing a valuable contribution to this problem.

Each chapter is well summarized and enhanced by a very comprehensive bibliography. This monograph also contains an excellent author and subject index.

G. H. Y.

The Medical Writings of Anonymus Londinensis. By W. H. S. JONES, Litt.D., F.B.A. 168 pages; 22 × 14 cm. Cambridge University Press, Macmillan Co., New York. 1947. Price, $2.75.

In this book the writer gives the complete Greek text and translation of a Greek medical papyrus, whose code name is Anonymus Londinensis. It was written in the second century A.D. in the style of a student comparing various authorities and schools of thought. Anyone who enjoys reading Hippocrates will appreciate this fragment. The author accompanies it with brief, but scholarly essays on Greek thought and medicine, as well as a carefully documented introduction to this text. This book represents a real addition to the source material of Greek medicine.

H. W. N.

Recent Advances in Endocrinology. 6th Ed. By A. T. CAMERON. 443 pages; 13.5 × 21 cm. Blakiston Company, Philadelphia. 1947. Price, $6.00.

This book continues to present a well chosen, well organized and well presented condensation of a number of significant articles on endocrinology. The author discusses the anatomy, function and clinical aberrations of the various endocrine glands. To the physician who desires to acquaint himself with the present scientific or clinical concepts of glandular disorders, it will prove highly valuable, and it will serve admirably as a reference to anyone interested in endocrinology.

Modern Dermatology and Syphilology. 2nd Ed. By S. WILLIAM BECKER, M.D., Clinical Professor of Dermatology, University of Chicago, and MAXIMILIAN E. OBERMAYER, M.D., Clinical Professor and Chairman of the Department of Dermatology, University of Southern California. 1017 pages; 18.5 × 26 cm. J. B. Lippincott Co., Philadelphia. 1947. Price, $18.00.

This second edition of *Modern Dermatology and Syphilology* has been greatly enlarged and many new additions are to be found.

It is worthy of note that in the chapter on Dermatologic Diagnosis the authors have presented several means of fixing and staining tissue, one of which, the dioxan method, is relatively new and apparently quite satisfactory.

The formulary has been amplified to include a number of preparations not mentioned in the previous edition and the formulae have been given for all of the compounds listed.

The general text is quite comprehensive and the various clinical descriptions are supplemented by the use of numerous photographs most of which are excellent.

The general chapter on syphilis is acceptable provided that the individual bears in mind the fact that the methods of syphilo-therapy are continually changing and that, unfortunately, most of the material appearing in textbooks is somewhat dated as it leaves the press.

The authors have revised their chapter on tropical cutaneous diseases and have amplified it to cover some of the more common things seen in World War II.

This new edition is far superior to the previous work.

H. M. R., JR.

BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Conference on Metabolic Aspects of Convalescence—Transactions of the Fifteenth Meeting. Edited by EDWARD C. REIFENSTEIN, JR., M.D. 163 pages (loose-leaf); 23 × 14.5 cm. (paper-bound). Josiah Macy, Jr. Foundation, New York. Price, $2.25.

Coronary Heart Disease. By A. CARLTON ERNSTENE, M.D., Chief of the Section on Cardiovascular Disease, Cleveland Clinic. 95 pages; 22.5 × 14.5 cm. 1948. Charles C. Thomas, Springfield, Illinois. Price, $2.50.

Crystalline Enzymes. 2nd ed. By JOHN H. NORTHROP, MOSES KUNITZ and ROGER M. HERRIOTT. 352 pages; 24 × 16 cm. 1948. Columbia University Press, New York. Price, $7.50.

The Digestive Tract in Roentgenology. By JACOB BUCKSTEIN, M. D., Assistant Professor of Clinical Medicine, Cornell University Medical College, etc. 889 pages; 26.5 × 18.5 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, $16.00.

Diseases of the Chest, Described for Students and Practitioners. 2nd ed. By ROBERT COOPE, M.D., B.Sc., F.R.C.P., Hon. Physician, Royal Liverpool United Hospital (Liverpool Royal Infirmary), etc. With a Foreword by LORD HORDER. 541 pages; 22.5 × 14.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $7.50.

Essentials of Fevers. 2nd ed. By GERALD E. BREEN, M.D., B.Ch. (N.U.I.Dub.); D.P.H., D.O.M.S. (R.C.P.Lond., R.C.S.Eng.), Tempy. Divisional Medical Officer, Hospitals Division, the London County Council, etc. 351 pages; 19.5 × 13 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $4.50.

Gardiner's Handbook of Skin Diseases. 5th ed. Revised by JOHN KINNEAR, O.B.E., T.D., M.D., M.R.C.P. (Ed.), D.L., Lecturer in Disease of the Skin, St. Andrews University, etc. 250 pages; 19.5 × 13 cm. 1948. The Williams and Wilkins Company, Baltimore. Price, $4.50.

Interesting and Useful Medical Statistics. Edited by WILLIAM H. KUPPER, M.D. 528 pages; 23.5 × 16 cm. 1948. William C. Brown Company, Dubuque, Iowa. Price, $6.50.

An Introduction to Dermatology. 11th ed. Formerly by NORMAN WALKER, Kt., M.D., LL.D., F.R.C.P., and G. H. PERCIVAL, M.D., Ph.D., F.R.C.P.E., D.P.H. 11th Edition by G. H. PERCIVAL, Grant Professor of Dermatology, the University of Edinburgh, etc. 349 pages; 22 × 15 cm. 1947. The Williams and Wilkins Company, Baltimore. Price, $9.00.

An Introduction to Physical Methods of Treatment in Psychiatry. 2nd ed. By WILLIAM SARGANT, M.A., M.B. (Cantab.), M.R.C.P., D.P.M., Physician, Maudsley Hospital, etc., and ELIOT SLATER, M.A. M.D. (Cantab.), F.R.C.P., D.P.M., Physician in Psychological Medicine, National Hospital, Queen Square, etc. With a Chapter on Treatment of the Epilepsies by DENIS HILL, M.B. (Lond.), M.R.C.P., D.P.M., Physician in Psychological Medicine, King's College Hospital, etc. 215 pages; 22 × 14 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $3.50.

Laboratory Diagnosis of Protozoan Diseases. 2nd ed. By CHARLES FRANKLIN CRAIG, M.D., M.A. (Hon.), D.Sc. (Hon.), F.A.C.S., F.A.C.P., Colonel, United States Army Medical Corps, Retired, etc. 384 pages; 24 × 15.5 cm. 1948. Lea & Febiger, Philadelphia. Price, $6.50.

Manual for Laboratory Work in Mammalian Physiology. By FRED E. D'AMOUR and FRANK R. BLOOD. Loose-leaf, unnumbered pages; 21.5 × 28 cm. 1948. University of Chicago Press, Chicago. Price, $2.75.

Medical Research in War: Report of the Medical Research Council for the Years 1939–1945. Committee of Privy Council for Medical Research—Presented by the Lord President of the Council to Parliament by Command of His Majesty, December, 1947. 455 pages; 24.5 × 15.5 cm. (paper-bound). 1948. H. M. Stationery Office, London. Price, 7s. 6d. net.

The 1947 Year Book of Pathology and Clinical Pathology. Pathology edited by HOWARD T. KARSNER, M.D., Professor of Pathology, Director of the Institute of Pathology, Western Reserve University. Assistant Editor: HERBERT Z. LUND, M.D., Assistant Professor of Pathology, Western Reserve University. *Clinical Pathology* edited by ARTHUR HAWLEY SANFORD, M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation), etc. 558 pages; 18.5 × 12.5 cm. 1948. Year Book Publishers, Inc., Chicago. Price, $3.75.

Physiological Therapy in Respiratory Diseases. 2nd ed. By ALVAN L. BARACH, M.D., Associate Professor of Clinical Medicine, Columbia College of Physicians and Surgeons, etc. 408 pages; 24 × 15.5 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, $9.00.

Psychiatry in a Troubled World: Yesterday's War and Today's Challenge. By WILLIAM C. MENNINGER, M.D., General Secretary, The Menninger Foundation, Topeka, Kansas, etc. 636 pages; 24.5 × 16 cm. 1948. The Macmillan Company, New York. Price, $6.00.

Temporary Rise in the Frequency of Thyrotoxicosis in Denmark, 1941–1945. By KURT IVERSEN. 244 pages; 25.5 × 17.5 cm. 1948. Rosenkilde and Bagger, Copenhagen. Price, Dan. Cr. 15.

Treatment of Heart Disease. By WILLIAM A. BRAMS, M.S., M.D., Ph.D., Associate Professor of Medicine, Northwestern University Medical School, etc. 195 pages; 24 × 15.5 cm. 1948. W. B. Saunders Company, Philadelphia. Price, $3.50.

War, Politics, and Insanity. By C. S. BLUEMEL, M.A., M.D., F.A.C.P., M.R.C.S. (Eng.). 121 pages; 21 × 13.5 cm. 1948. The World Press, Inc., Denver. Price, $2.00.

COLLEGE NEWS NOTES

Research Fellowships—The American College of Physicians

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1949–June 30, 1950. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for proper pursuit of his work. The stipend will be from $2,200 to $3,200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1948. Announcement of the awards will be made as promptly as is possible.

The American College of Physicians Establishes the A. B. Brower Traveling Scholarship

At the San Francisco Annual Session of the College, the Board of Regents on April 18, through the generosity of Dr. A. B. Brower of Dayton, Ohio, who made a subscription of $10,000, established "The Dr. A. B. Brower Traveling Scholarship Fund," which according to the conditions of the gift provide that "the income shall be used for the payment of expenses, in whole or part, of a deserving and promising young physician for attendance for a short period of time, for observation and study, at an outstanding institution of medical teaching, research or practice, such beneficiaries to be chosen and such institutions to be designated from time to time by the Board of Regents of the College." It is anticipated that a beneficiary will be selected annually, provided a suitable candidate can be selected and provided adequate income is available. The Committee on Fellowships and Awards will consult with the beneficiary as to the institution to be attended by him and the work which he especially desires to observe. It is felt that through the instrumentality of the College and its Committee on Fellowships and Awards exceptional opportunities may be provided not otherwise available to young men.

Elections to the American Board of Internal Medicine

The Board of Regents of the American College of Physicians has re-appointed for a term of three years Dr. Alex. M. Burgess of Providence, R. I., and Dr. Truman G. Schnabel of Philadelphia, Pa. Dr. Chester M. Jones of Boston, Mass., was also appointed to the Board for a term of two years, to fill out the unexpired term of Dr. William S. McCann, resigned.

At a recent meeting of the American Board of Internal Medicine Dr. Hugh J. Morgan, Nashville, Tenn., was elected Chairman, Dr. Marion A. Blankenhorn, Cincinnati, Ohio, Vice-Chairman, and Dr. Truman G. Schnabel, Philadelphia, Pa., was elected Secretary-Treasurer.

Dr. Wesley W. Spink Appointed Acting Governor for Minnesota

Due to the illness of Dr. Edgar V. Allen, President Walter W. Palmer has appointed Dr. Wesley W. Spink, of Minneapolis, as Acting Governor of the College for the State of Minnesota, the appointment beginning as of June 1.

Committee on Nominations, 1948–49

In accordance with ARTICLE I, Section 3, of the By-laws, President Walter W. Palmer has appointed the following to serve on the Committee on Nominations for 1948–49:

Maurice C. Pincoffs (Regent), Baltimore, Md., *Chairman*
A. B. Brower (Regent), Dayton, Ohio
Harold H. Jones (Governor), Winfield, Kans.
Chester S. Keefer (Governor), Boston, Mass.
T. Homer Coffen (Fellow-at-large), Portland, Ore.

Specialty Board Notice

The American Board of Pediatrics, Inc., 718 Royal Union Bldg., Des Moines, Iowa; Lee F. Hill, M.D., Secretary-Treasurer. Examinations will be held in Seattle, Wash., September 10–12, and in Atlantic City, N. J., November 17–19, 1948. The written portion of these examinations will be held on July 30, 1948.

University of California Medical School Offers Postgraduate Courses

Dr. Stacy R. Mettier, F.A.C.P., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California, announces the following courses offered in 1948:

Diseases of the Chest, given in collaboration with the American College of Chest Physicians and Stanford University School of Medicine; September 13 through 17; fee, $50.

Psychiatry and Neurology, at the Langley Porter Clinic; full time, 12 weeks, August 30 through November 19; fee, $200.

A.C.P. Course in Gastro-Enterology To Be Given at University of California and Stanford University, San Francisco

Drs. Theodore L. Althausen and Dwight L. Wilbur have agreed to organize and direct a course in Gastroenterology for the American College of Physicians at the Medical Schools of the University of California and Stanford University, San Francisco, during the week of February 7 to 12, 1949.

The Michael Reese Hospital Postgraduate School, Chicago, Ill., will offer an intensive postgraduate course in Electrocardiography under Louis N. Katz, M.D., M.D., F.A.C.P., August 16 to 28, 1948. Tuition will be $150.00.

The University of California at Los Angeles will offer a course in the Application of Nuclear Physics to the Biological and Medical Sciences, August 2 to 20, 1948. The fee for the lecture series alone is $100.00 and for the complete course, including laboratory training, $350.00. Enrollment is limited and applicants must present biographical data for approval by an official committee. Among the subjects treated in this course are methods of measurement of radioactivity, production of radioactive substances, principles of radiochemistry, applications of radioactive tracers, biological, therapeutic and genetic effects of radiation, and health protection and safety.

Northwestern University Medical School will offer a 5-day orientation course in allergy under the sponsorship of the American Academy of Allergy, October 25 to 29, 1948, inclusive. The course will comprise a complete and practical coverage of the subject and will utilize teachers not only from Northwestern University, but also from other medical schools. For particulars direct communications to Department of Allergy, Northwestern University Medical School, Chicago.

The Council on National Emergency Medical Service of the American Medical Association met in Chicago on April 5 and 6, 1948, with Ernest E. Irons, M.D., F.A.C.P., representing the American College of Physicians. More than 125 representatives of medical societies, national health and disaster groups and the armed services were present. Among the subjects discussed were medical implications of modern warfare, rôle of military and civilian groups and the need for services and physicians. In response to the request of the Army, Navy and Air Force for the Council's advice with respect to the needs for expanding the medical program of the Services and preparing for possible emergency contingencies, the Council recommended a six-point program as follows: 1. A single medical examination for screening, induction and assignment of selectees; 2. Withholding of induction of medical officers until actually required for medical care of military patients; 3. Adoption by the Services of a similar relationship with civilian medical facilities and personnel in the United States to that which is accomplished by the Veterans Administration's medical program; 4. Equal status for civilian medical reserve officers and career medical officers; 5. Continuation throughout the emergency of medical education and essential research; 6. Establishment of a National Emergency Medical Board as an agency of the National Security Resources Board.

In a survey it was found that only seven states had active programs for disaster relief. Efforts will be made to stimulate action in this respect.

The Council went on record as opposing proposed legislation to induct physicians by compulsion of law into the armed forces. The Council also affirmed that, in view of the possibilities of modern weapons, it would be unsafe to lower the ratio of civilian physicians to the 1-to-1500 ratio which was reached in the last war.

Observations on Postgraduate Course No. 5, Internal Medicine, Washington, D. C., May 17–22

The course in Internal Medicine was held at the Gallinger Municipal Hospital under the Directorship of Dr. Wallace M. Yater, F.A.C.P. Eighty-seven enrollees appeared for the course. All of the instructors appeared and gave their appointed lectures. The panel on Postwar Problems of Tropical Diseases, under Dr. Thomas A. Heidicke as moderator, was unusually interesting because of the presence of the following guest speakers: Dr. P. C. Sen-Gupta of Calcutta, India; Dr. Hamilton H. Anderson of San Francisco, Calif.; Dr. B. G. Maegraith of Liverpool, England; and Dr. Henry A. Meleney of New York City.

Ward rounds were made on the last afternoon and a question period was arranged at the end of most of the lectures. A new experiment in the course this year was the holding of an informal quiz on coronary heart disease at the end of one of the sessions. The men were so interested that they remained long after the appointed closing hour. Such informal quizzes prove extremely profitable. It is also desirable to have a larger proportion of clinical teaching and the Director expresses the intention of extending this type of teaching in future courses offered for the College. A smoker and reception was held at the end of the first afternoon session for the purpose of getting the group acquainted.

Veterans Administration Approves ACP Courses

The Department of Public Instruction of Pennsylvania, which is the official approving agency for the Veterans Administration in that State, has issued official approval of all postgraduate courses offered by the American College of Physicians on its autumn, 1948 schedule. This approval, however, covers veterans residing in the State of Pennsylvania, and it should facilitate their collection of fees for these courses.

This approval does not affect other states than Pennsylvania, but the College may later obtain approval of the other states, so that members of the College from whatever state in which they live may enjoy the same privileges.

A.C.P. Educational Committees Recommend Greater Dissemination of Information Among Physicians Concerning the Medical Aspects of Radioactivity

At a combined meeting of the Advisory Committee on Postgraduate courses and the Committee on Educational Policy of the American College of Physicians at the San Francisco Session during April, the following resolution was adopted: Resolved, The American College of Physicians shall encourage authorities in the field of radioactivity to prepare editorials which may be published in the Annals of Internal Medicine; that directors of various ACP courses be requested to schedule discussions by authorities on the use of isotopes; that the College explore further the development in this field through contact with already established courses, such as given by the Army, Navy, and certain of our universities; that the chairman of regional meetings be requested to schedule, when possible, lectures and/or demonstrations on the medical aspects of atomic energy.

Fourth International Congresses on Tropical Medicine and Malaria, Washington, D. C., May 10–18, 1948

More than 1000 delegates from 44 countries attended the Fourth International Congresses on Tropical Medicine and Malaria which were sponsored by the United States Government through the Department of State. Joseph M. Hayman, Jr., M.D., F.A.C.P., Cleveland, participated in the Congresses as official representative of the American College of Physicians.

The Congresses included the following sections: Research and Teaching Institutes, Tropical Climatology and Physiology, Bacterial and Spirochetal Diseases, Virus and Rickettsial Diseases, Malaria, Helminthic Diseases, Protozoan Diseases, Nutritional Diseases of the Tropics, Tropical Dermatology and Mycology, Tropical Veterinary Medicine, Public Health, and Medical and Veterinary Entomology. While many of the papers presented consisted of reviews of work already published, several were reported to be of particular interest. Dr. H. E. Shortt described the demonstration of pre-erythrocytic stages of *P. cynomolgi* infection in the parenchymal liver cells of monkeys and similar findings in one case of *P. vivax* infection of man, establishing a long sought link in the history of malaria infection. Dr. A. S. Alving reviewed studies of pentaquine in the treatment of South Pacific vivax malaria. Concurrent administration of 0.010 gm. of pentaquine base and 0.33 gm. of quinine sulfate every 4 hours throughout the 24 hours, for 14 days, has reduced the relapse rate from 98 per cent after suppressive drugs to about 25 per cent, in experimental volunteers. Relapses were reduced to 2 per cent after a second therapeutic course.

Newer developments in the therapy of leprosy with the sulfones were discussed by Dr. Robert G. Cochrane, of India, and by Drs. F. A. Johansen, F.A.C.P., USPHS, and P. T. Erickson, USPHS. Chaulmoogra oil has been entirely abandoned in favor

of the sulfones, which are of low toxicity and may be administered safely enterally and parenterally. Bromine must be given intravenously whereas diasone and promizole have the advantage of being tolerated well orally. The sulfone drugs are not claimed to be specific remedies, nor are spectacular cures to be expected. Almost universal improvement has followed their use. Definite objective improvement, with reduction of bacilli in the leprous lesions and simple atrophy of the morbid anatomical changes in the skin and mucous membranes, does not appear until after three to six months.

Distinctly encouraging results in the treatment of filariasis were reported by the use of arsenamide and hetrazan.

Official languages of the Congresses were English, French and Spanish, and as papers were delivered they were translated into the other languages and heard by headphone and radio.

A special exercise on May 12 commemorated the demonstration by Walter Reed of the mosquito transmission of yellow fever. Major General Raymond W. Bliss, (MC), USA, F.A.C.P., opened the meeting, and Philip S. Hench, M.D., F.A.C.P., gave the address of the evening. In another special meeting the fiftieth anniversary of the discovery of the method of transmission of malaria by Ross was commemorated.

At the Plenary Session Leonard A. Scheele, M.D., F.A.C.P., Surgeon General of the U. S. Public Health Service, was elected President, and Colonel Charles F. Craig, (MC), USA, Ret'd, F.A.C.P., was elected an Honorary Vice-President.

Additional Life Members

The College takes pleasure in announcing that by recent subscription the following Fellows became Life Members of the American College of Physicians: Edward A. Brethauer, Jr., Pittsburgh, Pa.; Harold H. Golz, Dhahran, Saudi Arabia; Theodore S. Heineken, Bloomfield, N. J.; Paul M. Rike, Pittsburgh, Pa.

A meeting of the Joint Committee for the Coördination of Medical Activities was held in Chicago on March 6, 1948. The American College of Physicians was represented by Dr. Walter L. Palmer, F.A.C.P., and Dr. Ernest E. Irons, F.A.C.P., both of Chicago. The latter serves as Chairman of the Committee. The discussions and actions taken at the meeting were fully reported in the Journal of the American Medical Association, May 15 issue.

At recent meetings, Euclid M. Smith, M.D., F.A.C.P., Hot Springs, Ark., was chosen President-Elect of the Arkansas Medical Society, and Charles H. Sprague, M.D., F.A.C.P., Bridgeport, Conn., was elected to the post of President-Elect of the Connecticut State Medical Society.

Esmond R. Long, M.D., F.A.C.P., Philadelphia, Pa., Director of the Henry Phipps Institute of the University of Pennsylvania and Director of Medical Research and Therapy of the National Tuberculosis Association, has been designated as Editor in Chief of the American Review of Tuberculosis. He succeeds in this position the late Max Pinner, M.D., F.A.C.P. Walsh McDermott, M.D., F.A.C.P., Associate Professor of Medicine in the Cornell University Medical School, has been appointed to the new position of Managing Editor of the Review. The editorial offices are being returned from Oakland, Calif., to New York City.

Dr. William B. Bean (Associate), of the University of Cincinnati College of Medicine, has been appointed Professor of Medicine and head of that Department at the State University of Iowa, Iowa City, assuming his duties on or about August 1, 1948. He succeeds the late Dr. Fred Smith, F.A.C.P.

Chester N. Frazier, M.D., Dr.P.H., F.A.C.P., Professor of Dermatology and Syphilology in the University of Texas School of Medicine and formerly of the Peiping Union Medical College, has been appointed Professor of Dermatology in the Harvard Medical School.

Alexander S. Wiener, M.D., F.A.C.P., Brooklyn, N. Y., has contributed to the College Library of Publications by Members a bound volume of his reprints of scientific articles.

James L. McCartney, M.D., F.A.C.P., Garden City, N. Y., has been elected President of a newly formed Nassau Neuropsychiatric Society which has been organized by private practicing neurologists and psychiatrists of Nassau County, N. Y.

Harold W. Kohl, M.D. (Associate), Tucson, was elected President of the Arizona State Medical Association at its annual meeting held recently in Phoenix. Robert S. Flinn, M.D., F.A.C.P., and Frank J. Milloy, M.D., F.A.C.P., both of Phoenix, were elected President-Elect and Secretary, respectively. Dr. Milloy also serves as Editor of Arizona Medicine.

Hyman I. Goldstein, M.D. (Associate), Camden, N. J., was official delegate of The National Gastroenterological Association and The New Jersey Gastroenterological Society to the Third National Congress on Cancerology which was held in Havana, Cuba, May 2–7, 1948. He was elected an honorary member of the Cuban Dermatological Society and a corresponding member of the Cuban Cancer Society. During his visit he delivered several papers before medical meetings.

A 16 mm., 3½ reel, sound motion picture in color entitled "The Role of Gastroscopy in the Diagnosis and Treatment of Gastric Pathology," has been produced for Leo L. Hardt, M.D., F.A.C.P., Clinical Professor, Department of Medicine, Loyola University School of Medicine. The film describes Dr. Hardt's studies of the human stomach, both normal and pathological, and the ability to follow the course of gastric pathology. With the aid of the gastroscope, Dr. Hardt and his associates have been able to develop a new anti-acid and to study the effect of this new anti-acid in the healing of gastric ulcers. The photography in this film is a combination of X-ray pictures indicating pathology with overlays of gastroscopic views of that pathology, the X-ray serving to locate points of infection. Inquiries concerning the film should be addressed to Harrower Laboratory, Inc., 920 E. Broadway, Glendale, Calif.

OBITUARIES

DR. GEORGE CHAMBERS ANGLIN

Dr. George Chambers Anglin died at his home in Toronto on April 14, 1948, from coronary thrombosis.

Dr. Anglin was born in Cork, Ireland, in 1890. He came to Canada in 1907 and graduated in Medicine from the University of Toronto in 1914. At the outbreak of World War I he was in England beginning post-graduate work but returned to Canada and joined the Royal Canadian Army Medical Corps. He was invalided home after three years of service and began the practice of internal medicine in Toronto. He became interested in pulmonary tuberculosis and respiratory diseases in general and joined the Chest Clinics of the Toronto Western Hospital and the Christie Street Military Hospital.

In World War II he became a consultant in diseases of the chest to M.D. 2 and to the Royal Norwegian Air Force in Toronto. He received the Haakon VII Medal of Liberation from the King of Norway in recognition of his services. At the time of his death, he was serving as Chief of the Chest Clinic of the Department of Veterans Affairs in Toronto.

Dr. Anglin became a Fellow of the American College of Physicians in 1931. He was a member of the Laennec and Trudeau Societies, the American Academy of Allergy, the American College of Allergists, the American College of Chest Physicians, and a diplomate of the American Board of Internal Medicine.

Possessed of a genial personality and impelled by a natural interest in people, Dr. Anglin was also endowed with unusual ability and as a result he reached a high level in the field of medicine and was a strong influence in the improvement of medical practice in this country.

H. K. Detweiler, M.D., F.A.C.P.,
Governor for Ontario

DR. LOUIS H. BEHRENS

Dr. Louis H. Behrens was long a teacher of medicine in St. Louis and one of the prominent figures in the practice of internal medicine. He gave unsparingly of his time and energy to organized medicine in St. Louis and served as president of the St. Louis County Medical Society which was an important force in the education of the average doctor.

Born July 12, 1868, Dr. Behrens acquired the degrees of Ph.G. from the St. Louis College of Pharmacy in 1888, and of M.D. from the Missouri Medical College in 1894. He served on the staffs of the Missouri Medical College and the Barnes Hospital for many years. He held commission during World War I as Captain in the U. S. Army Medical Reserve Corps. Dr. Behrens became a Fellow of the American College of Physicians in 1924, and a diplomate of the American Board of Internal Medicine in 1937.

For many years prior to his death on January 1, 1948, he had been incapacitated but had retained his contact with medical interests. He outlived most of his associates and friends, but is still vividly remembered. He achieved a definite position in the estimation and affection of his surviving associates.

R. A. Kinsella, M.D., F.A.C.P.,
Governor for Missouri

ABRIDGED MINUTES OF THE COMBINED EXECUTIVE SESSION OF THE BOARD OF REGENTS AND BOARD OF GOVERNORS

SAN FRANCISCO, CALIF.

APRIL 18, 1948

The combined Executive Session of the Board of Regents and Board of Governors was called to order at 2:15 p.m. in Room 203 of the Civic Auditorium, San Francisco, Calif., Sunday, April 18, 1948, with President Hugh J. Morgan presiding, and Mr. E. R. Loveland acting as Secretary.

President Morgan announced that after the taking of the roll, the two Boards would conduct their proceedings by separate action, but invited the members of both Boards to participate in discussions. Roll call showed the following in attendance:

Officers and Regents: Hugh J. Morgan, *President*; Walter W. Palmer, *President-Elect*; Reginald Fitz, *First Vice President*; Francis G. Blake, *Second Vice President*; Charles T. Stone, *Third Vice President*; William D. Stroud, *Treasurer*; George Morris Piersol, *Secretary-General*; Walter B. Martin; William S. Middleton; James E. Paullin; LeRoy H. Sloan; George F. Strong; William S. McCann; T. Grier Miller; Charles F. Moffatt; Charles F. Tenney; David P. Barr; A. B. Brower; Alex. M. Burgess; Ernest H. Falconer; Cyrus C. Sturgis; Maurice C. Pincoffs, *Editor,* ANNALS OF INTERNAL MEDICINE; Walter L. Palmer, *Chairman, Board of Governors.*

Governors: E. Dice Lineberry, Birmingham, ALABAMA; Fred G. Holmes, Phoenix, ARIZONA; Lewis B. Flinn, Wilmington, DELAWARE; Turner Z. Cason, Jacksonville, FLORIDA; Samuel M. Poindexter, Boise, IDAHO; Morris Flexner, Louisville (ALTERNATE), KENTUCKY; Eugene H. Drake, Portland, MAINE; John G. Archer, Greenville, MISSISSIPPI; Ernest D. Hitchcock, Great Falls, MONTANA and WYOMING; Asa L. Lincoln, New York, NEW YORK (Eastern); Marion A. Blankenhorn, Cincinnati, OHIO; Homer P. Rush, Portland, OREGON; M. D. Levy, Houston, TEXAS; Karver L. Puestow, Madison, WISCONSIN; Harold A. Des Brisay, Vancouver, B. C. (ALTERNATE), ALBERTA, BRITISH COLUMBIA, MANITOBA, SASKATCHEWAN; Leland Hawkins, Los Angeles, CALIFORNIA (Southern); Ward Darley, Denver, COLORADO; Walter Weissenborn, Hartford (ALTERNATE), CONNECTICUT; WALLACE M. Yater, Washington, DISTRICT OF COLUMBIA; Cecil M. Jack, Decatur, ILLINOIS (Southern); Robert M. Moore, Indianapolis, INDIANA; Harold H. Jones, Winfield, KANSAS; Chester S. Keefer, Boston, MASSACHUSETTS; Joseph D. McCarthy, Omaha, NEBRASKA; Edward C. Reifenstein, Sr., Syracuse, NEW YORK (Western); Wann Langston, Oklahoma City, OKLAHOMA; Edward L. Bortz, Philadelphia, PENNSYLVANIA (Eastern); R. R. Snowden, Pittsburgh, PENNSYLVANIA (Western); John L. Calene, Aberdeen, SOUTH DAKOTA; William C. Chaney, Memphis, TENNESSEE; Louis E. Viko, Salt Lake City, UTAH; Harry L. Arnold, Honolulu, HAWAII; Arless A. Blair, Fort Smith, ARKANSAS; Dwight L. Wilbur, San Francisco, CALIFORNIA (Northern); Benjamin F. Wolverton, Cedar Rapids, IOWA; Edgar Hull, New Orleans, LOUISIANA; Douglas Donald, Detroit, MICHIGAN; Frank J. Heck, Rochester (ALTERNATE), MINNESOTA; Ralph A. Kinsella, St. Louis, MISSOURI; Lawrence Parsons, Reno, NEVADA; Harry T. French, Hanover, NEW HAMPSHIRE; A. J. V. Klein, Newark (ALTERNATE), NEW JERSEY; Verne S. Caviness, Raleigh (ALTERNATE), NORTH CAROLINA; W. E. G. Lancaster, Fargo (ALTERNATE), NORTH DAKOTA; Robert Wilson, Jr., Charleston, SOUTH CAROLINA; Ellsworth L. Amidon, Burlington, VERMONT; Charles M. Caravati, Richmond, VIRGINIA; George Anderson, Spokane, WASHINGTON; Delivan A. MacGregor, Wheeling, WEST VIRGINIA; Arthur T. Henderson, Montreal, QUEBEC; George C. Beach (ALTER-

NATE), UNITED STATES ARMY; John Harper (ALTERNATE), UNITED STATES NAVY; G. A. Abbott (ALTERNATE), UNITED STATES PUBLIC HEALTH SERVICE.

Guest: William J. Kerr, Co-General Chairman, San Francisco Session.

The Secretary read abstracted Minutes of the preceding meeting of the Board of Regents, which were approved as read.

President Morgan called upon the Secretary to present communications, as follows:

(1) A letter from Dr. A. B. Brower, Regent, of Dayton, Ohio, tendering a donation of $10,000.00 for the founding of a traveling fellowship in medicine, the income from which shall be used for the appointment annually of a deserving and promising young physician for attendance for a short period of time, for observation and study, at an outstanding institution of medical teaching, research or practice, the beneficiary to be chosen and the institution to be designated from time to time by the Board of Regents of the College.

. . . On motion by Dr. James E. Paullin, seconded by Dr. George Morris Piersol, a resolution was adopted, accepting the gift with the greatest appreciation, "a very substantial and practical stimulus to the attainment by the College of one of its important missions and purposes." . . .

(2) A notice from the American Board of Internal Medicine to the effect that the following appointees' terms, by the Board of Regents of the American College of Physicians, to the American Board of Internal Medicine will expire on June 30, 1948, and that new appointments shall be made:

Dr. Truman G. Schnabel
Dr. Alex. M. Burgess

Also, due to the resignation of Dr. William S. McCann, as of June 30, 1948, a new appointee should be nominated for his unexpired term, to June 30, 1950.

. . . President Morgan requested that the Committee on Educational Policy, headed by Dr. William S. Middleton, Chairman, bring to the next meeting of the Board of Regents names of nominees for these three vacancies. . . .

(3) A letter of appreciation from the Secretary of the Regents of the University of Wisconsin, stating that the fees amounting to $1,975.00, transmitted by the College to the University of Wisconsin, covering a recent Postgraduate Course under the direction of Dr. William S. Middleton, had been accepted by the Regents of the University and credited to the Medical Library Building Fund.

(4) A report that President Hugh J. Morgan had appointed Dr. William S. McCann as representative of the College at ceremonies in Rochester, N. Y., January 12, 1948, in connection with the Regional Blood Program of the American Red Cross.

(5) A report of the appointment by President Hugh J. Morgan of Dr. George Morris Piersol, as College representative, on the Executive Committee of the President's Committee on "National Employ the Physically Handicapped Week."

(6) A letter from Dr. Paul R. Hawley, resigning from the College Governorship of the Veterans Administration, concurrent with his retirement as Medical Director of that Service, and announcement of the interim appointment by President Hugh J. Morgan of Dr. Arden Freer as Governor for the Veterans Administration.

(7) An announcement of the appointment of Dr. Ernest H. Falconer as College representative to the Pacific Regional Conference of UNESCO.

(8) An announcement of the appointment by President Hugh J. Morgan of Dr. Walter W. Palmer and Dr. George Morris Piersol as College representatives on the First International Poliomyelitis Conference.

(9) An announcement of the appointment by President Hugh J. Morgan, by authorization of the Board of Regents, of a Committee to consult with the Committee of the American Medical Association, the American College of Surgeons, and hospital

associations, concerning means by which nursing education and other services may be furthered, the Committee of the College consisting of Dr. Francis G. Blake, Chairman, Dr. Walter W. Palmer and Dr. Thomas P. Murdock.

(10) An announcement of the appointment by President Hugh J. Morgan of Dr. Ernest E. Irons as College representative to attend a two-day meeting of the Council on National Emergency Medical Service, April 5–6, at Chicago, and to bring any matter of importance to the Regents at San Francisco.

. . . (Dr. Irons was absent at the Regents' meeting, and there was no report.) . . .

PRESIDENT HUGH J. MORGAN: The reports relative to the above appointments have been received and filed, or will be received for review if there are any matters that need the attention of the Regents at a subsequent meeting. We shall refer the resignation of Dr. Paul R. Hawley to the Committee on Nominations, so that a permanent successor may be nominated at the proper time.

The next item will be a report from Co-Chairmen Kerr and Falconer on the San Francisco Session.

DR. WILLIAM J. KERR: On behalf of the Fellows, Regents and Governors in California and all the Western States, we welcome you to San Francisco. We think we have a good program, some entertainment that will please you. Beginning tonight there will be some entertainment at the combined dinner of the Regents and Governors; there will be a Symphony Concert tomorrow night. The scientific program is, we believe, an excellent one, with morning lectures, panel discussions, clinics, inspection tours, general sessions, etc. We expect to give you some real live clinics, and we have arranged the programs so that morning lectures and clinics will not conflict. We open our arms to you and bid you welcome.

DR. ERNEST H. FALCONER: . . . If there is anything any of you want to do not listed on the program, just make your wishes known to me and I shall try to fulfill them while you are here.

PRESIDENT MORGAN: On behalf of the Governors and Regents, I think this is the appropriate time to express our thanks to Dr. Kerr and Dr. Falconer for arranging what is obviously going to be an outstanding meeting of the College.

We shall now receive the report of the Secretary-General, Dr. George Morris Piersol.

. . . Dr. Piersol reported that since the last meeting of the Board of Regents there had been recorded the deaths of 43 Fellows and 5 Associates, whose names were spread upon the Minutes; also that since the last meeting of the Board 78 additional Fellows have become Life Members, making a grand total of 708, of whom 51 are now deceased, leaving a balance of 657. The names of these new Life Members were, likewise, spread upon the Minutes. . . .

. . . Special mention was made of the name of Dr. Samuel E. Munson, who had served a long time as the Governor of the College for southern Illinois; the members of the Board stood in silence in respect to the deceased members. . . .

PRESIDENT MORGAN: May we now receive the Memorial on Dr. Fred W. Wilkerson, prepared by Dr. Walter B. Martin and Dr. Walter L. Palmer.

DR. WALTER B. MARTIN: This is in memoriam of Dr. Fred W. Wilkerson, and is in the form of a resolution:

"The Board of Regents of the American College of Physicians records with sorrow the loss of one of the distinguished members of the American College of Physicians, Dr. Frederick Wooten Wilkerson.

"Doctor Wilkerson, the son of a physician, exemplified the best in the traditions of our profession. His interests were broad and won him a place of high honor, not only in the strictly professional field, but as a leader in organized medicine. As President of his state society, a member of the House of Delegates of the American Medical Association, and as the representative of his State on the Board of Governors of the American College of Physicians for many years, he served the interests of our

profession, and of the general public. His life and works may well be an inspiration to those that come after him.

"The Board of Regents of the American College of Physicians therefore RESOLVES that this expression of our appreciation of his contributions to our profession and to society be spread on our permanent records, and that a copy be sent to his family."

PRESIDENT MORGAN: Next we shall receive a Memorial on Dr. Ernest B. Bradley, former Governor and former President, prepared by Dr. James E. Paullin and Dr. David P. Barr.

DR. JAMES E. PAULLIN: "WHEREAS, Ernest Brennan Bradley, A.B., M.D., M.A.C.P., who had served the American College of Physicians as a member of the Board of Governors, as a member of the Board of Regents, and as its President (1936–37), was called by death on November 12, 1947, and

"WHEREAS, Dr. Bradley was known to the members and in particular to the official family of the American College of Physicians as a leader in his profession, with unusual powers for organizing and promoting educational programs for the advancement of medical training and knowledge, and

"WHEREAS, his wisdom and farsightedness, together with his lovable attributes, stimulated and encouraged those with whom he was associated, and

"WHEREAS, during his term of office as President of the American College of Physicians, through his guidance and planning, the scientific meetings of the College were expanded in scope, and the usefulness of the College was broadened by the establishment of regional meetings, all of which evidenced his abiding faith in the position which the College must assume as a medium of promoting better medical care, now, THEREFORE, be it

"RESOLVED, that we, the members of the Board of Regents, being deeply conscious of the great loss in his death to the American College of Physicians, and to the medical profession of his state, deplore his passing, and that we record this tribute to his memory, and be it FURTHER

"RESOLVED, that a copy of these resolutions be transmitted to his family as evidence of our deep love and affection for him, and as an expression of our sympathy in their loss and bereavement."

PRESIDENT MORGAN: Next we shall receive a Memorial on Dr. John H. Musser, former Regent and former President, prepared by Dr. William S. Middleton and Dr. T. Grier Miller.

DR. WILLIAM S. MIDDLETON: "JOHN HERR MUSSER (1883–1947). In this day of professional materialism it is refreshing to review the career of a man whose life was dedicated to medicine. John Herr Musser, a Philadelphian by birth, was the son of an eminent clinician and the sixth in direct line in this profession. Had he set about to pursue his career upon the established chart of his remarkable heritage, he could not have steered a truer course.

"With a firm foundation of secondary education at the William Penn Charter School and of academic training in the College of the University of Pennsylvania, John Musser entered upon the study of medicine. His undergraduate medical work at the University of Pennsylvania School of Medicine marked him as a worthy successor to his medical forbears. His father was a distinguished Professor of Clinical Medicine in the University while he was pursuing his studies. Upon his graduation from the School of Medicine (1908), John Musser served his internship for six months at the University Hospital and two years at the Pennsylvania Hospital. Thereupon a short period of graduate study was spent at the University of Amsterdam. Returning to Philadelphia, he was associated with his father in the practice of medicine, until the latter's death (1912). Three institutions in Philadelphia, Howard Hospital, Philadelphia General Hospital and Presbyterian Hospital, gained greatly by his attendance upon the medical services. As Associate in Medicine (1914–20) and Assistant

Professor of Medicine (1920–24), John Musser gave unstintingly of his talents to undergraduate medical instruction in his Alma Mater. Under his direction new life was given to the Outpatient Service and teaching in the University Hospital. His normal career was interrupted by two years of military service in World War I Nor did his interest in military medicine cease with the termination of hostilities. He maintained his Reserve Corps affiliation to become a colonel in 1938. However, the return to private practice in Philadelphia found the pace a killing one and the opportunities for independent effort and study limited by its exactions. Accordingly, John Musser left Philadelphia to become Professor of Medicine at Tulane University of Louisiana School of Medicine in 1924. His interest in Pennsylvania never waned. He served as a graduate representative on its Board of Trustees. In recognition of his services and of his eminence in medicine he was granted the Award of Merit by the University (1940).

"Arriving in New Orleans when forty-one years old, John Musser found certain challenges that only his tact, poise, and tenacity of purpose could have surmounted. His post was the first full-time professorship in a clinical field in a proud Southern university. Furthermore, internal medicine was not developed or practiced in the accepted sense of a specialty in any measure in New Orleans. Opposition in high places was inevitable. With characteristic imperturbability John Musser bent his unselfish energies to the task of creating one of the best departments of medicine in the United States. Soon his patent integrity and measured enthusiasm won increasing allegiance from the medical students and from the younger staff members. His background of clinical and laboratory research insured the firm foundation of his department at Tulane; but his profound human interest and keen clinical instinct held him close to the bedside, where his fine analytical mind found full expression and outlet in the training of young internists.

"John Musser was a big man in every sense of the word. His warm personality permeated every gathering to which he lent his presence. Yet he did not sacrifice his high principles to mere social advantage. When the lines were drawn in support of the health and well-being of the children of Louisiana, John Musser's position was clearly stated, even though the red herring of state medicine was aligned with the immunization program. Without thought of personal sacrifice he gave one-half of his time (1940–42) to assist in the reorganization of the Louisiana State Board of Health. As a fitting tribute to his effort in another cause the new unit for tuberculous patients at Charity Hospital had been named for him.

"John Musser early demonstrated a literary flair. Over one hundred and fifty medical articles came from his pen. In the main they dealt with clinical subjects; but his earlier contributions to the physiology and the pathology of the spleen are noteworthy. Significantly he made a special study of 'The Heart That Is Ageing.' His assistant (1911–20) and chief editorship (1920–24) of the American Journal of the Medical Sciences marked a season of remarkable growth in this standard periodical. Upon his transfer to Louisiana he became Editor of the New Orleans Medical and Surgical Journal (1927) and he served on the Editorial Board of the Archives of Internal Medicine for some years. His earliest venture in medical textbook publication was the editorship of four editions of his father's 'Practical Treatise on Medical Diagnosis.' After several further excursions into this field he undertook a major project in the publication of 'Internal Medicine, Its Theory and Practice' (1932), which ran through its fourth edition in 1945.

"Many medical organizations profited by John Musser's active participation in their scientific deliberations and administrative affairs. In addition to the local and regional societies to which he contributed so materially, he was active in the American Medical Association, the Association of American Physicians, the College of Physicians of Philadelphia, the American Clinical and Climatological Association, the American Society of Clinical Investigation, and the American College of Physicians.

In all candor it may be said that to none of these groups did he give more abundantly than to the American College of Physicians. His Fellowship in the College dated from 1920. He served as Regent from 1926 to 1936. He became President-Elect at the Twelfth Annual Clinical Session at New Orleans (1928) and President the following year. The College was experiencing a renaissance at the time and through the stabilizing influence of such men as John Musser came the implementation of earlier reform movements. John Musser strove for the consolidation of effort. Through an economy of existing agencies and personnel a three-fold objective of the College was fixed. In his judgment better standards of admission to Fellowship, rehabilitation of the educational program and improvement of the official organ of the College required immediate attention.

"In the evolution of the plans for the certification of internists John Musser's leadership and vision made him a logical nominee from the American College of Physicians for the formation of the original American Board of Internal Medicine. In its ultimate organization, however, it became expedient that his nomination come from the Section on the Practice of Medicine of the American Medical Association. In no other capacity did the fine statesmanly qualities of John Musser stand in better stead than in the organization and early operation of the American Board of Internal Medicine. The minutes of the meetings of this Board until the expiration of his third term of service (July 1, 1945) reflect the clarity of his vision and his keen interest in the advancement of American medicine. The composition of the Founders' Group, the policy of certification without examination, and the conduct of special examinations for candidates in the Armed Services assigned to overseas duty are a few marks of these qualities. Contemplative always John Musser would allow a discussion to pass without comment. Occasionally he would make a note and then with a fine analysis of the intricacies of the problem, for the first time he would offer his own opinion of the situation. In retrospect it is singular how frequently his motion or amendment carried.

"In the very nature of the man, it was inevitable that John Musser should have been so regularly sought in support of public works, both regional and national. His membership on many committees, lay and professional, commonly led to his chairmanship or presidency in the same. Yet never was there a feeling of aggression. His associates deferred to his natural leadership and unobtrusively John Musser took such responsibilities without offense to the participating members. His patent sincerity and integrity stilled all reservations. His qualities of friendship were as well developed as his talents of leadership. With fine sensitivity he avoided friction. His consideration for his fellowman was a measure of the secret wells of his strength. His humanity and profound interest in people led to personal sacrifices of time and energy he could ill afford. Yet always the kindly touch and the unaffected personal absorption in his associates made the occasion one of warm mutual understanding rather than a perfunctory issue. In the years when physical limitations were imposed by his growing infirmity, John Musser never lost his fine philosophy. He refused to bow to his handicap. In spite of a major disability he persisted in his manifold interests within the limits of his physical capacity until a second invader finally overwhelmed his stalwart body. Never did the stout spirit waver. His courage and fortitude sustained him to the end. Gentleman unafraid, teacher-clinician extraordinary, medical statesman supreme, Master of the American College of Physicians, John Musser will be a figure long remembered and revered in American medicine."

PRESIDENT MORGAN: These three Memorials are fine expressions of the feelings and admiration and affection that we hold in our minds and hearts for these great physicians and late fellow members of this College. The Regents and Governors are indebted to the authors for these Memorials.

We shall next have the report of the Committee on Credentials by Dr. George Morris Piersol, Chairman.

. . . Dr. Piersol reported the Committee on Credentials had held two meetings since the last meeting of the Board of Regents, the first on February 28, 1948, and the second on April 17, 1948. The report was long and detailed, and out of it grew the following actions: Dr. L. Clagett Beck, Honolulu, T. H., was granted an extension of his Associate term for a period of two years; Dr. Maxwell R. Berry, Jr., of Atlanta, Ga., and Dr. Edmund L. Shlevin, of Brooklyn, N. Y., were reinstated to Associateship, each for a term of one year. . . .

. . . Dr. A. B. Brower, a former Governor and at present a member of the Committee on Credentials, was requested to appear before the Board of Governors to explain the very effective plan he followed while Governor in investigating candidates for membership. The Committee recommended that special steps be taken to encourage the several Governors of the College to investigate candidates more thoroughly through other Fellows or Masters in their respective territories. . . .

. . . 104 Fellows and 195 Associates were elected (these names were published in the June, 1948, issue of this journal). . . .

. . . Of the candidates elected to Associateship five years previously, namely, April 4, 1943, and whose five-year terms, under normal circumstances, would expire during the spring of 1948, 30 had qualified for advancement to Fellowship; 26 had received extension of time, because of military service; and 9 had failed to qualify and were dropped from the Roster, in accordance with provisions of the By-Laws, and their names were recorded in the Minutes; also the names of the 26 physicians having extended Associate terms were recorded in the Minutes. In addition, the Committee recorded the names of 6 Associates who were elected prior to April 3, 1943, whose terms had previously been extended because of military service, but whose terms at this time expired without their qualifying for Fellowship, and they were consequently dropped. . . .

PRESIDENT MORGAN: This represents an extraordinary amount of work on the part of this Committee, work accomplished in the most careful fashion. We all desire to express our appreciation. A more important Committee cannot exist in this College.

We shall now have a report from the Committee on Constitution and By-Laws by Dr. James E. Paullin, Chairman.

DR. JAMES E. PAULLIN: The By-Laws of the College were amended at the 1947 Annual Session of the College, and, among other things, provided a new Article VI for the election of Masters, in which it is specified, "a special Committee on Masterships will be named by the President. This Committee will consist of two members from the Board of Regents and one member from the Board of Governors. It will bring in nominations of Masters to the Board of Regents for election or rejection."

That amendment makes it necessary for an amendment to the Constitution, Article IV, (b), substituting in line 5, "Committee on Masterships" in the place of "Committee on Credentials." Namely, this paragraph shall be amended to read:

"Masters of the American College of Physicians shall be those who have attained the rank of Fellows, and who on account of personal character, positions of influence and honor, eminence in practice or in medical research, or other attainments in science or in the art of medicine, are recommended by the Committee on Masterships to the Board of Regents for special and well-earned distinction. Such Masters shall be designated as Masters of the American College of Physicians, and shall be authorized to use the letters M.A.C.P. in connection with scientific publications, at professional and academic functions and in connection with their professional activities."

This amendment shall be submitted to the members at the next Annual Business Meeting at San Francisco, April 22, 1948, for approval.

. . . On motion duly made, seconded and carried, the above amendment to the Constitution was approved, with the recommendation that it be approved at the Annual Business Meeting for final change and correction. . . .

PRESIDENT MORGAN: Next will be the report of the Committee on Fellowships and Awards by Dr. Reginald Fitz, Chairman.

DR. REGINALD FITZ: As recorded in the Minutes of the previous meeting of the Board of Regents, this Committee nominated seven men for Research Fellowships, beginning July 1, 1948, and for this purpose $20,460.00 was appropriated. At the time the Committee met it felt that in the event of any of the candidates being unable to accept the fellowship offered, the Committee would prefer not to make any substitute nominations, and any excess fund should be returned to the fellowship pool. Since the last meeting we have received word that one of our appointees, Dr. Joseph E. Giansiracusa, has decided not to accept the fellowship. Therefore, the Committee recommends that the $3,200.00 thus released be returned to the fellowship pool.

. . . On motion by Dr. Maurice C. Pincoffs, seconded by Dr. Alex. M. Burgess, the recommendations of Dr. Fitz were unanimously approved. . . .

PRESIDENT MORGAN: We shall now have the report of the House Committee by Dr. William D. Stroud, Chairman.

DR. WILLIAM D. STROUD: The new building project is essentially completed and is now occupied. The only remaining things to be done are the putting up of venetian blinds in the first and second floors, the installation of screens and the replanting of the lawn. Financial statement follows:

Original Contract (R. M. Shoemaker Co.)	$47,980.00
Additions:	
1 Extra Radiator (Pindar's Office)	192.00
Removal of varnish and refinishing old woodwork, 1st floor	375.00
Entrance, Basement	409.75
	$48,956.75*
Architect's Fee, 6%	2,937.41*
Other Additions:	
Electric Fixtures	413.42
Venetian Blinds and Shades	350.00
Screens	325.00
Landscaping (Plantings)	564.30
Rubber and Plastic Floorings	1,332.00
Refinishing Rear Stairs	275.00
TOTAL CONTRACTED COST	$55,153.88
APPROPRIATION	55,000.00
DEFICIT	$ 153.88

* Payments during progress:

12–3–47 Contractor	$20,277.00
1–1–48 Architect	1,919.20
1–1–48 Contractor	8,757.90
2–14–48 Contractor	7,938.00
3–11–48 Contractor	4,879.80
TOTAL Paid to April 7, 1948	$43,771.90
Balance Due Architect	1,018.20
Balance Due Contractor	7,104.05

The whole addition is considered eminently satisfactory and fine, an addition to the Headquarters of which everyone will be proud. Of prime importance is the fact that the Executive Offices now have full and ample room for efficient work and adequate space for internal expansion over many years to come.

The entire staff is now organized on the first floor, with the exception of the Addressograph and Duplicating Departments, which are on the basement level. An excellent meeting room, with facilities to accommodate more than one hundred individuals, is on the second floor. It is anticipated that this room may be used for Regional Meetings, Postgraduate Courses, and other purposes. There appears no immediate need to consider the purchase of suitable chairs for this meeting room until autumn, or at the pleasure of the Board of Regents. Possibly the room may be left as is until the next meeting of the Board of Regents, at which time decision may be made concerning its furnishings.

PRESIDENT MORGAN: Anyone who has had anything to do with building recently will certainly be impressed with the fact that our Committee has stayed within the budget, with the exception of $153.88. It will require action by the Regents relative to this deficit.

. . . On motion by Dr. David P. Barr, seconded by Dr. Reginald Fitz, and unanimously carried, the Board of Regents appropriated $153.88 to cover this deficit. . . .

PRESIDENT MORGAN: This is the end of the agenda for the Regents' meeting and the Chair relinquishes his position to Dr. Walter L. Palmer, Chairman of the Board of Governors.

. . . Dr. Walter L. Palmer, Chairman, assumed the Chair, and called to order the meeting of the Board of Governors.

CHAIRMAN WALTER L. PALMER: Dr. Morgan, we thank you and the Board of Regents for your great courtesy in inviting the Governors to meet with the Board of Regents today. We shall, first, have the reading of abstracted Minutes of the last meetings of this Board.

. . . The Secretary, Mr. E. R. Loveland, read an abstract of the Minutes of the three meetings of the Board of Governors held during the 1947 Annual Session. There were no corrections, and the Minutes were accepted as read. . . .

CHAIRMAN PALMER: We shall proceed to the receipt of reports from Committees. The first will be from the Governors' Committee of Five on proposals concerning methods of elections of Officers, Regents and Governors, Dr. Edgar V. Allen, Chairman.

DR. FRANK J. HECK (ALTERNATE for Dr. Allen): Dr. Allen is ill and has been away for a number of weeks. Unless Dr. Wolverton, another member of the Committee, has some definite information, I know nothing about the report of this Committee.

DR. BENJAMIN F. WOLVERTON: Dr. Allen, as Chairman of this Committee, sent out a questionnaire to all the Governors last winter. However, I have heard nothing from Dr. Allen since that time, and I would suggest a delay in the report from this Committee until our next meeting.

CHAIRMAN PALMER: We shall consider this a report of progress, and defer it until a future meeting.

The next Committee report is that of the Advisory Committee on Postgraduate Courses, Dr. Edward L. Bortz, Chairman.

DR. EDWARD L. BORTZ: Mr. Chairman, our current spring schedule of courses is operating as follows:

Course No. 1—MEDICAL ASPECTS OF RADIOACTIVITY
U. S. Naval Medical School
Bethesda, Md.
February 18–27, 1948—

has been concluded, with a registration of 22 from the College, augmented by a considerable number of Naval and Military Officers. The course was received with enthusiasm. In view of the importance of the new and rapidly expanding

field of atomic energy and its bearing on medical science, this Committee this morning expressed the opinion that the College should stress the importance of members taking every opportunity to inform themselves concerning this rapidly expanding field. The Committee recommends that from time to time editorials be presented in the ANNALS OF INTERNAL MEDICINE, written by such authorities as Dr. Stafford L. Warren, and other men in the forefront of this field, in order that our members shall keep abreast of developments. Furthermore, the Committee is of the opinion, and desires to recommend, that for the various courses of the College, where possible, there be invited to the faculty an authority in the field of atomic energy, as it applies to particular specialties.

The Committee desires to recommend that contacts be established with those schools and centers of graduate training, such as several of the medical schools, the group in Chicago, and the appropriate departments of the Army and Navy, in order to enlarge the opportunities for College members to take advantage of this instruction. Also, the Committee recommends for your consideration, that the various Regional Meetings which you Governors organize include on the program something in the field of atomic energy. Such an outstanding authority as Dr. Shields Warren has made a statement that this (atomic energy) is the most important and significant development in medical science since the discovery and the development of the microscope. In view of the unsettled state of affairs of the nation and the possibility of future involvement, the medical profession certainly, and surely the authorities and leaders of organized medicine, are obligated to know about the potentialities, the dangers that are inherent in the possible use of atomic bombs. Whether or not it would be utilized in a national emergency, or whether or not a catastrophe should occur in other ways, the medical profession should know its responsibility. I am sorry to say that from my contacts and from my travels throughout the land, I confidently believe that our medical profession is very inadequately informed about the dangers inherent in atomic energy and the handling of radioactive isotopes. That is one phase.

Another phase, and even more important, concerns the researches going on. Your Committee is of the opinion that every possible channel for instruction of the membership of the College should be developed and encouraged to facilitate better understanding of the basic principles and the details inherent in both radioactive and stable isotopes.

About two years ago the College was the first organization, I believe, to offer a course in radioactive isotopes. A small group of possibly ten or twelve men came to the Research Department of the Lankenau Hospital in Philadelphia to study, and all of them stated that their work there was highly beneficial, and they hoped the course would be repeated. With that in mind, we pursued the possibility of having our members attend courses given by the Navy Department in Washington and accomplished that end. We believe in the future we shall be able to continue to send men to special courses given by the Army and Navy, by the University of Chicago and other institutions.

Course No. 2—PHYSICAL MEDICINE FOR THE INTERNIST
Mayo Clinic and Mayo Foundation for Medical Education and Research
Rochester, Minn.
March 22–26, 1948—

Dr. Frank H. Krusen, F.A.C.P., Director; registration 17, supplemented by a number of local physicians.

Course No. 3—Cardiovascular Diseases
University of Southern California School of Medicine
Los Angeles, Calif.
April 12–17, 1948—

Dr. George C. Griffith, F.A.C.P., Director; registration 47; a very popular course.

Course No. 4—Electrocardiography: Basic Principles and Interpretation
Massachusetts General Hospital
Boston, Mass.
May 10–15, 1948—

Dr. Conger Williams, Director; registration limited to 26.

Course No. 5—Internal Medicine
Gallinger Municipal Hospital
Washington, D. C.
May 17–22, 1948—

Dr. Wallace M. Yater, F.A.C.P., Director; present registration 74; capacity 100.

Course No. 6—Clinical Allergy
Roosevelt Hospital
New York, N. Y.
May 17–28, 1948—

Dr. Robert A. Cooke, F.A.C.P., Director; registration limited to 8.

Course No. 7—Clinical Neurology
Jefferson Medical College of Philadelphia
Philadelphia, Pa.
May 24–29, 1948—

Dr. Bernard J. Alpers, F.A.C.P., Director; present registration 38; capacity 75.

Course No. 8—Physiological Basis for Internal Medicine
University of Illinois College of Medicine
Chicago, Ill.
May 31–June 5, 1948—

Dr. A. C. Ivy, F.A.C.P., Director; current registration 180; capacity 200. With such a large registration, this course becomes more of a convention than a graduate course. This is unfortunate, because the objective of our courses should be for the student-physician to come into close intimate contact with the teacher. This is the second time we have given this course, the first one being given with sensational success under Dr. Julius H. Comroe, Jr., of Philadelphia.
We believe interest in the basic fundamentals on which medicine is practiced has been stimulated in a very generous measure by the insistence of the American Board of Internal Medicine that men be well grounded in the basic sciences.

Course No. 9—Diabetes and General Medicine
New England Deaconess Hospital
Boston, Mass.
July 12–16, 1948—

Dr. Elliott P. Joslin, F.A.C.P., Director; current registration 35; capacity 75. This is our first experience in arranging summer courses, and it is probable that this course will be filled to capacity.

Now reporting on the 1948 schedule of courses already approved by the Board of Regents, but subject to some alteration, we propose the following:

. . . (Dr. Bortz outlined the proposed courses for the autumn of 1948 in considerable detail, but inasmuch as this Roster of courses has been published elsewhere in this journal, it is not repeated here.) . . .

There are other courses under consideration. I want to say something about psychosomatic medicine. A very successful one-week course was given a year or so ago by Dr. Franklin Ebaugh, and the Committee has waived the advisability of another course. We are of the opinion that to split off one particular small specialty in a larger, important field is probably not in the tradition of our program. We are looking forward, not this year, but perhaps next year, to give a course in psychiatry, with the consideration of psychosomatic medicine as it fits into that field.

Then in 1949 we are keeping in mind enlarging the opportunities for more instruction in the Physiological Basis for Internal Medicine and the Mechanics of Disease. We shall have courses in hematology, cardiology and other fields, and if the Governors have any suggestions or comments, the Committee will be grateful for them.

. . . On motion by Dr. William D. Stroud, seconded by Dr. M. D. Levy, the report of the Committee was accepted. . . .

CHAIRMAN PALMER: The next on our agenda is a report from the Executive Secretary on Regional Meetings.

. . . Mr. E. R. Loveland, Executive Secretary, distributed a duplicated outline of all Regional Meetings held during 1947 and to date in 1948, or scheduled later in 1948. . . .

CHAIRMAN PALMER: The Governors will recall that at the last meeting of the Board there was considerable discussion of the relative merits of large multi-State Regional Meetings, as contrasted with the small single State Regional Meeting, and I think it was concluded that these two types of meetings each have their special merits and advantages, as well as disadvantages. It was mutually agreed to leave the decision to the men in each territory to decide which type of meeting they prefer.

The only remaining item on the agenda for this session is a group of announcements, which will be made by the Secretary at the end of the meeting. I wish now to turn the meeting back to President Morgan.

. . . Pesident Morgan resumed the Chair. . . .

PRESIDENT MORGAN: The Committee on Credentials has a matter which they would like to bring to the attention of this combined meeting, and I shall ask Dr. George Morris Piersol to take the floor.

DR. PIERSOL: These matters are only in the form of suggestions, and there are a great many arguments pro and con that may be advanced. These suggestions are presented by the Credentials Committee for discussion, not with the object of lightening their own troubles and burdens in passing upon candidates. However, because of the feeling of inadequacy which they experience continually, and because of difficulty in arriving at accurate and definite conclusions in regard to the qualifications of certain candidates, these suggestions have been prepared. It was suggested from time to time, over a number of years, by various members of the Credentials Committee that it might be best to exclude from the College those who, although closely affiliated with internal medicine, are not primarily internists, such as neuropsychiatrists, dermatologists, or some other affiliated specialists whose fields are set forth in our informative booklet. Heretofore, we have always taken them. Their number grows, not excessively, but steadily, and with this increment, the size of the College, likewise, grows steadily.

It has been assumed that the College is not interested in becoming an enormous group, but rather to make it an adequate, compact and representative body of those represented in internal medicine.

In order to bring this or any other change about, it is going to be necessary to amend the By-Laws. It is a cumbersome and important matter that must be carefully

considered. The suggestion is to eliminate at some specified future time from admission to membership those groups who, though affiliated with medicine rather than surgery, are not primarily internists. This could be done without subjecting them to any serious inconvenience. They all have their own extremely efficiently functioning certifying boards and special societies in which they are very much interested. The groups particularly in mind are the radiologists, dermatologists, syphilologists, neuropsychiatrists, those in industrial medicine, and possibly pediatricians.

The second suggestion from the Credentials Committee is equally important and already has been a source of much discussion over the years. You will recall that less than five years ago it was suggested, brought up, discussed and voted down that one of the qualifications for admission to Associateship should be certification by the appropriate specialty board. This involves a principle which is quite basic, and there are those who believe in it heartily, and there are those who are equally vehemently opposed. It is my recollection that the Board of Governors previously did not look with favor upon such a change.

In order to meet the issues to some extent at least, a Survey Committee was appointed, under Dr. William S. Middleton, Chairman, which Committee brought in a very thoughtful and careful report. Their recommendations have been approved and have been incorporated in our By-Laws. The Credentials Committee is now doing its best to operate under those regulations. However, any of these regulations are subject to great variability and, as good as they are, constitute different yardsticks for application. It was, therefore, actually brought up by and instigated by, not only those who in the beginning advocated certification as a prerequisite for Associateship, but those previously vehemently opposed to the proposal, who, having watched over a period of years the uncertain workings, finally came to the conclusion that it is very difficult for a small Committee, or even for the Governors, to try to pass upon the eligibility of an individual. That involves the opinions of a good many people and variabilities are not controllable. If it were flatly stated, "if you are an internist, demonstrate the fact that you are a bona fide internist, both with intention and in your ability and in your professional attainment by appearing before the board and being certified," then there is no further necessity of exploring all sorts of collateral evidence to establish that the candidate is an internist, or ever going to be an internist.

It is only fair in discussing this matter to say that so thoughtful a person as Dr. Ernest E. Irons, who was unable to be here because he is absent from the country, wrote the following letter to the Executive Secretary, which was handed to the Credentials Committee at this meeting:

"(1) As I take it the purpose of the College is primarily the promotion of standards and education in the field of internal medicine. There are other considerations of fellowship, acquaintance and the stimulation of younger men by prospective membership which are, along with others, highly desirable.

There has been what seems to me an unfortunate creation of divisions of internal medicine which have developed with the rapid increase in special knowledge. Such divisions are unavoidable and indeed are desirable and necessary. However, these divisions into sub-specialties need not be carried into the question of standards of accomplishment in internal medicine. It is true that gastro-enterology is on perhaps a little different basis than radiology since radiology partakes in its interest both of medicine and surgery. I believe that the inclusion of the several groups such as pediatrics, neurology, psychiatry, pathology, etc., is really of great advantage to the College in broadening the viewpoint of the members.

"(2) The argument that the College is getting too large seems unfortunate, because as it is to be of maximum value to medicine, it should not become

a private group. If the membership is limited with a constantly expanding number of persons who are qualified for membership and still cannot enter, the situation is set up whereby other organizations will come into the field and we will create our own competition.

I am aware that carrying out the above policies will not solve the mechanical questions and labor of the Credentials Committee. This Committee has done marvelous service and is doing it, but I doubt the wisdom of changing the policy of the College in order to lighten the work of the Credentials Committee."

That, Mr. President, is the gist of the situation.

PRESIDENT MORGAN: You have heard these suggestions. Unless it is the will of the group that we take positive action on these two important questions, and they certainly are important, I would suggest that we here and now discuss these matters for thirty minutes and take no action until the next meetings of the Regents and Governors.

Of the two questions raised, I might say one really decides the other. If we should decide that certification shall be specifically by the American Board of Internal Medicine as a prerequisite for Associateship, the question of any candidates coming in from dermatology, neuropsychiatry, radiology, etc., will be automatically settled. If there are neurologists, for instance, who want to be internists as well and will come up before the Board of Internal Medicine, they would qualify insofar as that requirement is concerned.

DR. JAMES E. PAULLIN: Doesn't the report of the Survey Committee under Dr. Middleton last year settle this matter, insofar as the By-Laws are concerned?

DR. MIDDLETON: Only insofar as making certification necessary for Fellowship, not for Associateship, nor do the By-Laws specify the particular specialty board. Dr. Piersol's suggestion would limit this to the American Board of Internal Medicine, and would apply the rule to Associates as well as Fellows.

DR. LAWRENCE PARSONS: I have been a member of the Board of Governors for a few years, and I am one of those funny doctors, a pathologist, and have gotten a great deal of benefit from them. As long as there is nobody to speak for some of us, I should like to say a word or two in our behalf. It has been a pleasure for me to come here, and I have felt very proud, in a certain sense, to be associated with such a fine group of physicians. I always felt that a man who had "F.A.C.P." after his name held a certain amount of distinction. I am sure that is the general opinion of medical men. I hope that some of the specialties in medicine which are very intimately associated with internal medicine, such as pathology, will not be taken out of this organization.

It certainly has been most helpful to me to be associated with the College, and I hope that I will be allowed to remain. I should certainly like to see that clinical pathology of all things is not taken away from internal medicine. Anyone who reads the journals sees some of the finest contributions to clinical pathology from professors of medicine. Dr. Cecil Watson, for instance, has written many fine articles that have appeared in the American Journal of Clinical Pathology. On the other hand, clinical pathologists have published articles in the ANNALS OF INTERNAL MEDICINE and in the Archives of Internal Medicine.

PRESIDENT MORGAN: Thank you, Dr. Parsons. I am sure we feel the same about clinical pathologists.

DR. WILLIAM S. MCCANN: I think there is much wisdom in Dr. Irons' letter. We should not forget that the creation of the specialty boards has always created some special colleges. There would be a great disadvantage to American medicine if the general body of physicians, as distinguished from surgeons, were to be weakened by any more division. I think the College should keep its place as the representative

of the non-surgical part of the profession. It would be a grave mistake, in my opinion, to exclude any but certified internists from this body. I believe that the matter of certification will take care of itself in the future.

At the present time there are undoubtedly many able men who have established themselves well in their field of internal medicine, and who would be reluctant to tackle the present type of written examination by the boards. It would be too restrictive if we were to insist upon certification for admission to Associateship.

DR. PIERSOL: There still exists confusion of understanding. At the present time it is perfectly clear an Associate does not have to be certified. A candidate can come up for Associateship if he is an internist, or follows any of the subdivisions of internal medicine, or any of the affiliated branches of medicine. That is all, as it stands today. The new question is shall we continue to take in candidates who are following these affiliated subjects in medicine. We should make it clear that pathologists, biochemists, and all those engaged in the basic sciences should be included. I think the present problem mostly concerns the continued admission of dermatologists, syphilologists and radiologists, who are in very border-line specialties when it comes to internal medicine. At present no one has to be certified, unless he aspires to be a Fellow; and, if he is a neurologist, he must be certified by the American Board of Neurology and Psychiatry; if a dermatologist, by the American Board of Dermatology and Syphilology, and so on. There has never been the thought that if a man followed an allied specialty, such as neuropsychiatry or dermatology, he should be forced to take an examination by the American Board of Internal Medicine.

The present idea is to exclude from membership in the future, not making it retroactive, those who are not internists, but who practice some of the clinical specialties. It has nothing to do with the subspecialties of medicine. Then if we were to say we would take in only internists, regardless of their subspecialties, in order to clarify who is such a person and to have criteria that are accurate and workable, we would say that he ought to be certified by the American Board of Internal Medicine, "or his respective board," which would still have to be put in, because certainly no one would try to exclude the basic sciences, which form many foundations of internal medicine.

DR. WALLACE M. YATER: It might clarify the situation just a little to remind the members here that we cannot accept as Associates men who do not have the prerequisites, in our opinion, to be admitted to the board examinations. That is where the difficulty arises. The Credentials Committee is not in a position to decide, in many cases, whether a man has the prerequisites that the Board will require. It would be so much easier if the candidate had already taken his board examinations, because we would then have that information all settled. In other words, we think he should have his basic requirements before we can accept him as an Associate.

DR. E. DICE LINEBERRY: May I ask what the percentage is of the members in the allied specialty groups?

MR. LOVELAND: I cannot tell you specifically without checking the Membership Roster. There has been a steady increase in the number of candidates from some of the allied specialties, such as neurology and psychiatry. I would guess that we have among our members about three hundred neuropsychiatrists. There has been a definite decline in the number of pediatricians seeking membership. I think we have less than one hundred and fifty among our members. We haven't more than one hundred in the field of radiology. I should think we have no more than thirty or forty dermatologists, and very few physiologists.

DR. ALEX. M. BURGESS: We should be clear on anything we do on this subject. We are dealing with two separate topics—the question of elimination of certain allied fields of work, and the question of requiring certification as a prerequisite for Associateship. If we think back a little and realize the history of the College and its development throughout the years, we shall note that it has changed a great deal. The

efforts of the Board of Governors over a period of years have tended to bring in more distinguished men and keep out the less distinguished, and Associateship or Fellowship now represents a much greater distinction than it did twenty years ago. Now this College has created the American Board of Internal Medicine with its requirement for certification, which, as I see it, has come into direct conflict with Associateship. The members of the Credentials Committee are feeling that conflict, and it is up to us to clear the matter; if, as we now hope, the Board of Internal Medicine is able to investigate, properly screen out and certify all competent internists, it then seems to me that Associateship, as well as Fellowship, should be a step higher and a step further along in the career of a physician. That should be the ideal we strive for in the future. If that is carried out, it simplifies very greatly the practically impossible task to which the College is committed through its Credentials Committee, namely, the election of these men. I do not infer that the American Board of Internal Medicine can ideally select these men, but it is an agency for that purpose, and it is trying hard to do so. If certification becomes a prerequisite for Associateship, then the Committee on Credentials is freed from the conflicts, including determination of the candidate's real specialty, the follow-up on certification between Associateship and Fellowship, the careful checking of time limits, and so forth. It would simplify and greatly improve the situation, and would put the College on a level of greater distinction, increasing the value of the College to all concerned.

Dr. Turner Z. Cason: I am opposed to the sentiment just expressed. Does not the premise of the College indicate its purpose to be the extension of medical knowledge and the improvement of medicine? If we do what has been suggested, we shall be getting away to a certain extent from this very thing. A young fellow comes along, qualifies for Associateship and must immediately begin to work on preparation for his boards. We encourage him; we offer him graduate courses; we make reduced rates, and so forth. If we say he cannot become an Associate until he has passed the board, we are not helping him to do the very thing that we started out to do. I have another thought. In some communities the board is valued at more than the College—at least it is in some of the hospitals, and if we start excluding them that way, I am afraid they will pass the board and pay no further attention to the College. That is a phase worth considering. I think our plan has worked out best the way it stands now.

Dr. Burgess: I would like to answer just one point; perhaps that is the crucial issue, and Dr. Cason may be more right than I, but I should like to point out the following: a young man becomes an Associate, he has three years before he is eligible to become a Fellow, but he may be prevented, so easily by illness or something else, from taking the board examinations for say three years, and then if he fails the first time, he has a year left; if he fails the second time he cannot retake the examination for two years; his Associateship will have lapsed, and he will have been dropped from the College Roster. It seems to me if we keep our present plan, in all fairness to these candidates, they must have a longer period of Associateship, in order to qualify for Fellowship, in the now restricted five-year period.

Dr. Maurice C. Pincoffs: I wonder, if the Credentials Committee had the standard of certification before election to Associateship, if it would not find some difficulty in setting up adequate criteria for advancement to Fellowship. Is it not very helpful, under our present plan, to have this certification constitute one of the important criteria for Fellowship? Other and new criteria, it would seem to me, would put an added load on the Credentials Committee. I would like to find out what the Committee has in mind as specific criteria for passage from Associateship to Fellowship.

Dr. Piersol: The general principles are set forth in the regulations that were adopted following the Survey Committee's report. If you will read that over, you will get a good idea. I might say in passing that there is a steadily increasing number of proposals for Associateship from men who have already been certified. It is astonishing how that number has risen.

Now, certification is not synonymous with being elected a Fellow. If a man is certified, an internist, and otherwise qualified, in order to be advanced to Fellowship he must do one of several things: he must have shown adequate interest in furthering his medical career; he must have acquired some sort of hospital or teaching affiliation; and he must have contributed in some creditable manner to the literature. There are many candidates turned down who are certified, but who have never written or done anything of any note, and have not grown medically during their five years of Associateship. I do not suggest that the College should set up standards comparable to some of the very elite scientific groups, where a man must have demonstrated his ability to do original research or outstanding work of some other character before he is admitted, but in the College he must have shown some aptitude, some energy and some interest as expressed by the professional attainment in teaching or hospital appointment, or other public medical activity. He must have contributed, not merely a manuscript largely gathered from the textbooks of medicine and read at a staff meeting, but he must have really contributed something which a critical Editor would be willing to publish.

DR. JOSEPH D. MCCARTHY: I am of the impression that an Associateship in this College is a probationary period. Am I correct?

PRESIDENT MORGAN: Yes.

DR. MCCARTHY: I am thinking of the candidate who qualifies to take his board examinations. He becomes an Associate; he proceeds to attain certification. In the future some of these younger men will not be able to qualify as rapidly for certification, perhaps, as they have been the past few years. I quite agree that the Associate term should be a spur to that man, for him to know that he must go ahead and attain certification before he can become a Fellow.

DR. CHARLES F. TENNEY: I think it would be interesting to hear what percentage have already been certified before being proposed for Associateship this past year.

DR. PIERSOL: Approximately 75%.

PRESIDENT MORGAN: I wonder what the Canadian's experience has been. What about the Royal College in Canada and its attitude, Dr. Moffatt?

DR. CHARLES F. MOFFATT: Conditions up North are different from what they are here. We have one College, the Royal College of Physicians of Canada, to which there is one examination. There is no preliminary examination, although there is one minor part, and then the final examination, which admits to "F.R.C.P." We have no probationship. In comparing these examinations, we believe they are about on par with those of the American Board of Internal Medicine. The examination is the only requirement, apart from the usual rule of showing a certain number of papers and an aptitude for internal medicine, which follow very much the same rules as the American College. There are certain degrees which we accept in Canada, such as "F.R.C.P. of London," "F.R.C.P. of Edinburgh," and occasionally "F.R.C.P. of Ireland." It is not the intention to tighten the restrictions at the present time.

DR. LINEBERRY: How many candidates fail because of failure to attain certification, rather than for any other reasons?

DR. PIERSOL: Not too many, possibly less than 5%.

DR. LINEBERRY: If we wish to reduce the membership we could raise the age limit and do the same thing.

DR. PIERSOL: I may say that there have been two suggestions put forth—one that the age limit for Associateship be increased to 35, and another that the Associate term be extended for more than five years.

PRESIDENT MORGAN: Our time has expired, and, Dr. Palmer, with your permission, I will declare the meeting adjourned.

. . . The meeting *adjourned* at 5:15 p.m. . . .

Attest: E. R. LOVELAND,
Executive Secretary

ABRIDGED MINUTES OF THE BOARD OF REGENTS

SAN FRANCISCO, CALIF.

APRIL 20, 1948

The second meeting of the Board of Regents, held during the 29th Annual Session at San Francisco, Calif., was called to order at 1:15 p.m. in Room 203 of the Civic Auditorium on April 20, 1948, with President Hugh J. Morgan presiding, and Mr. E. R. Loveland acting as Secretary. The following were in attendance:

Hugh J. Morgan, *President;* Walter W. Palmer, *President-Elect;* Reginald Fitz, *First Vice President;* Francis G. Blake, *Second Vice President;* Charles T. Stone, *Third Vice President;* William D. Stroud, *Treasurer;* George Morris Piersol, *Secretary-General;* Walter B. Martin, William S. Middleton, James E. Paullin, LeRoy H. Sloan, George F. Strong, William S. McCann, T. Grier Miller, Charles F. Moffatt, Charles F. Tenney, David P. Barr, A. B. Brower, Alex. M. Burgess, Ernest H. Falconer, Cyrus C. Sturgis, Maurice C. Pincoffs, *Editor,* ANNALS OF INTERNAL MEDICINE; Walter L. Palmer, *Chairman, Board of Governors.*

The Secretary was ready to present a full transcript of the Minutes of the preceding meeting, but by resolution, seconded and duly carried, that was dispensed with.

Among communications presented to the Board were the following:

(1) A letter from Dr. Ernest E. Irons, reporting that he had attended two sessions of the Emergency Medical Service Committee on behalf of the College, and discussing the proceedings of the meeting. Several types of laws to be presented to Congress, concerning conscription, were discussed, but at that time it had not been possible for the doctors to present a firm statement, because they had not seen the proposed draft of the law. The discussion had hinged about the proposal to provide in the draft law for men up to 26 years of age, but to require a draft of physicians up to 45 years of age. The Committee on Emergency Medical Service had opposed this as being discriminatory and reflecting on the patriotism of the doctors.

. . . The discussion of this subject by the Regents was by direction omitted from the Minutes. . . .

(2) A letter from Dr. Noble Wiley Jones, regarding Honorary Fellowships. Dr. Jones submitted a communication to President Morgan advocating the establishment of honorary memberships or fellowships in the American College of Physicians, to honor distinguished men here at home or abroad, pointing out that the Royal Australasian College of Physicians had conferred Honorary Fellowships on two Fellows of the American College of Physicians, whereas the American College of Physicians has no machinery by which such compliments may either be returned or initiated.

President Morgan proposed that the matter be referred to the Committee on Constitution and By-Laws "for their consideration as to whether or not the College should create Honorary Fellowships, and, if so, provide the necessary amendments to the Constitution and By-Laws."

(3) A letter from Dr. Albert M. Snell, Rochester, Minn., concerning the stimulation of interest in the creation of an international society of internal medicine. Dr. Snell and Dr. David P. Barr had been invited to attend an organization meeting, and the sponsors of the movement had asked that the

American College of Physicians, the Association of American Physicians and the Society for Clinical Investigation be contacted and their interest solicited. Dr. Barr stated that he had been invited to attend and had replied that such an organization might find a useful function, but that he would be unable to take part in its organization. Dr. Barr expressed the opinion that perhaps this is an inappropriate time to undertake this venture.

President Morgan asked for general discussion.

DR. JAMES E. PAULLIN: Mr. Chairman, in view of the fact that we are organizing a World Medical Association, I move that this communication be referred to the Committee on Public Relations, and that they report back at the next meeting of the Board of Regents.

. . . The motion was seconded and regularly carried. . . .

(4) An announcement from Dr. Walter W. Palmer of the appointment of Dr. Walter L. Palmer, Chicago, as official representative of the College at the Conference on Nomenclature of Disease, meeting at the Headquarters of the American Medical Association on June 23, for the purpose of setting up committees and carrying out the necessary preliminary work toward the revision of the Standard Nomenclature of Disease and for its publication early in 1950.

(5) A letter from Dr. Lowell A. Erf, Chairman of the Scientific Exhibit Committee of the Centennial Celebration meeting of the Medical Society of the State of Pennsylvania, inquiring if the American College of Physicians would be interested in presenting an historical exhibit.

It was the sense of the meeting that the Secretary be requested to reply, stating the College is not in a position to provide an exhibit for this occasion.

(6) MR. E. R. LOVELAND: There were two communications in a manner related to one another—one was submitted through the College Governor for the Veterans Administration, pointing out that in many instances the regulations of the College preclude Veterans Administration physicians from qualifying for Fellowship in the College, for the simple reason that certification is a prerequisite, as well as membership in one's recognized state and national societies, including the American Medical Association. On the other hand, in certain localities, the American Board of Internal Medicine will not admit a physician to its examinations unless he is a member of the American Medical Association, and there are in some locations such regulations that a Veterans Administration physician may not join the local county and state medical societies, and thus is not eligible for membership in the American Medical Association. This matter has been placed before Dr. George F. Lull, General Secretary of the American Medical Association, and he has assured us that in June this situation may be remedied, extending to Veterans Administration doctors the same courtesies that at present are extended to Army and Navy physicians, allowing them to become members of the American Medical Association without necessarily membership in county and state medical societies.

The other communication originated from the College Governor for Panama and the Canal Zone, in which he points out that there is practically nothing that he can do, as Governor, toward presenting candidates for membership in the College from that area. Physicians in Panama and neighboring countries, and it is also true of Cuba or Mexico, or any other Central American country, are not eligible for admission to the examinations of the American Board of Internal Medicine, or any other certifying board, and, thus, could not comply with the certification requirement for advancement to

Fellowship in the College. That is, physicians not eligible for membership in the American Medical Association, therefore, cannot be admitted to the American Board examinations, and, therefore, under present regulations could never qualify for Fellowship in the College, yet it is our published regulation that a citizen physician of any North American country is eligible for College membership. The result of this situation is that physicians outside of the United States or Canada can only enter the College at present through direct Fellowship.

DR. MORGAN: Dr. McCann, will you speak on this from the point of view as Chairman of the American Board of Internal Medicine?

DR. WILLIAM S. MCCANN: This matter has been discussed in our meeting, and my recollection is that the feeling of the Board is that the requirements for admission to the examinations should be modified, in order to permit Veterans Administration doctors to come in. I do not remember hearing about any discussion of citizens from other countries, such as Panama, Cuba or Mexico.

DR. MORGAN: In order to bring this matter into complete focus from the point of view of the springboard from which the American Board approached it, I make this comment: in a certain state it costs $125.00 or $150.00 dues in the county medical society, and the American Board questions seriously if it had the right to insist that some young doctor in a Veterans Hospital, or any other activity, who wanted to be examined and was eligible from other standpoints, that he expend such a sum for county society membership before admission to the examinations. That was one practical feature of the matter. We consider this to be a very serious question.

DR. PAULLIN: I move that this communication be referred to the Committee on Public Relations for study, and that they report some recommendation at the next meeting of the Board of Regents. This is important, and we ought to study it.

. . . The resolution was seconded and regularly carried. . . .

(Communications continued):

(7) From Dr. Hugh J. Morgan concerning interpretation of regulations governing the Bruce Award.

DR. MORGAN: After consulting the Minutes of previous meetings, I recommend the following interpretation, subject to confirmation by the Board:

(1) Under ordinary circumstances traveling expenses of the recipient will be less than $125.00, in which case he shall receive a stipend of $125.00;

(2) In any case where the traveling expenses (such as in 1948 at San Francisco) exceed $125.00, there shall be no stipend to the recipient, but his traveling expenses, according to the normal allowances made, shall be paid in full by the College, the additional amount beyond $125.00 to be taken from the general funds of the College.

. . . On motion by Dr. Maurice C. Pincoffs, seconded by Dr. George F. Strong, the recommendations were unanimously approved. . . .

(8) From Dr. Hugh J. Morgan concerning traveling expenses of Governors to the Annual Sessions.

MR. LOVELAND: Dr. Morgan asked my office to analyze the cost, under varying circumstances, of paying to the Governors an allowance for travel to the Annual Sessions, similar to that paid to the Board of Regents; that is, the round trip train and pullman fares. Such an analysis has been made, and it shows that for Annual Sessions held in the east, middle west and far west, with Philadelphia, Chicago and San Francisco selected as typical cities, the cost at present would be as follows: Philadelphia, $7,472.00; Chicago, $6,454.00; San Francisco, $12,410.00.

DR. MORGAN: The idea that it would be well to explore this matter stemmed from agitation that grew out of the Board of Governors' meetings last year, relative of the importance of the Governors to the College, and the feeling on the part of a few that the Governors were really somewhat sidetracked and by-passed. It is extremely important that Governors be present for the Annual Meetings, but it is quite essential that the Regents, constituting the board of directors for the transaction of official management of the College, be present. The Governors are the field representatives of the College, the ones who more than any one else determine the quality of the membership, because they feed into the Credentials Committee the information which makes it possible for that Committee to act wisely on candidates. The Regents may favor in principle the handling of the matter of expenses of the Governors on the same basis as for the Regents. . . .

. . . There was general discussion headed by Dr. Alex. M. Burgess, Dr. Maurice C. Pincoffs, Dr. Charles F. Tenney, and others, favoring this action, if it is possible financially. On a motion by Dr. Burgess, seconded by Dr. Paullin, and carried, it was

RESOLVED, that the matter be referred to the Committee on Finance to study the feasibility of the plan, and to report back to the Regents.

(9) From Dr. Arthur J. Patek, F.A.C.P., relative to the matter of rebating of fees from laboratories.

DR. MORGAN: Dr. Patek wrote to the College relative to the matter of rebating of fees from laboratories, x-ray laboratories, clinical laboratories, and so forth, a matter about which we have been hearing so much in the newspapers recently. I would like the College to take official action which would lead to the withdrawal of the approval of hospital appointments of men who are known to accept such rebates. I wrote him unofficially that the matter would be brought to the attention of the Board of Regents, but pointed out that this College is not an operational organization in that sense, and that it is unlikely that our Board would take any formal action; that the Constitution and By-Laws of the College and Fellowship Pledge preclude acceptance by members of rebates, or fee splitting practices. Dr. Patek is much exercised about this matter and wrote a fine letter to the American Medical Association a few weeks ago, and he wants to do something about it.

MR. LOVELAND: Mr. President, there is a similar matter before the Committee on Public Relations at the present time.

DR. MORGAN: We can ask that this communication be answered by the Committee on Public Relations on the basis of their other recommendations, and we refer the matter, therefore, to that Committee.

May we now have a report from the American Board of Internal Medicine, Dr. William S. McCann, Chairman.

DR. MCCANN: Dr. Morgan and Gentlemen: At the last meeting of the Board of Regents we discussed the mechanism for the approval of hospitals for training. The question was raised of a joint action of some sort which would aid the Council on Medical Education and Hospitals in performing its task of survey and approval. A Liaison Committee was appointed, consisting of Dr. Reginald Fitz and Dr. LeRoy H. Sloan. The difficulty of the Council appears to be that of getting sufficient personnel to make the inspections, rather than the lack of funds. At our last meeting it was suggested that a panel of part-time inspectors be made available to the Council, and that these men be paid $50.00 per diem and expenses, according to the formula used in the Veterans Administration for their consultants and section chiefs. The method of selection for such a panel was not fully discussed. It was felt that inspectors could be, or should be, Fellows of the American College of Physicians and Diplomates of the American Board of Internal Medicine. How this panel should be drawn was left unsettled. Dr. Fitz may comment on this later.

Now we might say a word about the result of the American Board examinations. I believe that the Board is utterly convinced now that the present type of examination, the so-called written portion, is better than the old essay type, that it is more fair and more searching. Each new examination, as it has come along, has been set so as to eliminate flaws found in the previous ones. I believe about the same percentage of people pass this form of written examination as passed the old essay type.

With regard to the oral examination, our Board was better satisfied with the oral examination just held here in San Francisco than with any oral examination which I have attended in the seven years of my association with the Board. Curiously enough, a slightly greater number of men failed in this oral examination than was customary in previous examinations. Usually the rate of failures is between 25 and 30 per cent. It is estimated that about 40 per cent failed the current one.

Now, I believe this was a good examination. The place where it was held was extraordinarily well adapted to the purpose; that is, material was excellent, well studied and the records were fine. The moot questions coming up could be settled from the dates in the charts, and I think we had an unusually good chance to evaluate the candidates.

What are the implications of this? It shows that there is a considerable number of men who can pass a very difficult written examination, but may be quite inadequate at the bedside. The converse may also be true, that there may be some excellent doctors, clinicians and internists who would not do so well in a written examination. We ought to ask ourselves searchingly whether we are excluding some very desirable people by the very stiff written examination. I think we have to admit that a certain number of men fail because of nervousness. All of our examiners have encountered men with whose performance they were familiar, but who went to pieces under the strain of examination. By and large, I think the men who fail do so because they have been trained in institutions which lack the type of discipline that produces the really sharp internist.

That leads me to the next step in the procedure. The Board has considered that we should at this time tabulate our experience in the whole history of the Board, in order to determine what hospitals and training agencies had given up a large number of failures. I believe an arrangement will be made to carry out this study, and when we get this information, it could be utilized by the Council on Medical Education and Hospitals and by the Board in determining the question of future approval of institutions for training. The hospitals themselves, if they were aware of this fact, could take corrective measures. Perhaps all that one would need to do would be to publish the results in the American Medical Association's Journal, such as is done for the state board examinations, so that one can tell what percentage of graduates of a school fail in those examinations.

There is still under discussion the matter of holding small regional oral examinations in different parts of the country by only a part of the Board. That is, taking the members of the Board who reside in the region and holding the examinations on a smaller scale. That would permit us to utilize many excellent hospitals which are not big enough to accommodate the larger numbers, such as at our present examinations. That plan has many advantages and many disadvantages, which have led the Board to withhold their final decision.

It may be unnecessary to adopt this measure to deal with the backlog of unexamined candidates if we can repeat the oral examinations in the future as successfully as we have done here in San Francisco. The Board is very grateful to the local men who have provided us with such splendid facilities.

I shall be retiring from the Board as of June 30 of this year, after several years of service. I should like to pay a tribute to my colleagues on the Board. I have never seen a group of men who worked more wholeheartedly and more devotedly for the

cause of improving the training of internists and the practice of medicine. Never have I seen any evidence of any desire to restrict the number of men certified. The effort has been solely to improve the method of determining what the qualifications were. Our methods are admittedly somewhat imperfect, but I think that they have been steadily improving, and I have no doubt that further improvement will continue.

PRESIDENT MORGAN: Thank you, Dr. McCann, for a most interesting and fine report as the retiring Chairman of the American Board of Internal Medicine. It is only fair for me, one member of that Board, to say that much of the progress with relation to the technique of doing the job, which the Board feels constitutes a great responsibility, has been encouraged, if not actually developed, by Dr. McCann.

DR. MCCANN: Dr. Morgan, there was one question which troubled the Board for years, about which I would like to comment, because I think the Regents should be aware of our difficulties. This is the matter connected with subspecialty certification. The creation of subspecialty certification has been the most troublesome single problem of the Board. We have certain organizations in tuberculosis, allergy, etc., that are not satisfied with our solution of the matter. Our Board has always held that subspecialty certification in cardiology, gastroenterology and chest diseases should be based on the general qualifications of an internist. In the case of allergy, I think we can see that the same thing is true, but an allergist might be an internist, he might be a pediatrician, he might be a dermatologist, and there is, perhaps, something to be said for the dissatisfaction among the allergy group, which is drawn from at least three sources instead of only one. I feel the weight of the College and the Regents should be thrown behind the Board in this matter, and that we should strive to prevent the independent formation of boards in subspecialties.

It is my guess that that movement comes from the fact that there are older men who have been long established in certain special fields of practice who feel that it would be impossible for them to take such examinations as the American Board gives, and yet they feel they want some special label attached to them. I believe it would be helpful if we could get some general statement which indicates that we do not feel that the important thing is to put a label on the older men. What we are trying to accomplish through this Board is to help mold the men who are coming up and who will occupy those positions in the future, and to see that they have a good, broad, firm and general foundation when they do that. They are the important ones, not the older men. I do not know how such a point of view could be presented to the profession as a whole, but it might allay some of this restlessness of which we see manifestations.

DR. MORGAN: The request is that the Committee on Educational Policy take under consideration this topic just discussed by Dr. McCann, relative to the establishment of subspecialty boards, to study the matter during the months ahead, and bring to the next meeting of the Regents in November a general statement of policy as an expression of the College relative to this problem. Unless there is some feeling to the contrary, the Chair will request that the matter be referred to the Committee on Educational Policy, Dr. William S. Middleton, Chairman, with the request that such a statement be formulated and presented to the Board of Regents at its November meeting for action.

We shall now have a report of the Committee on Educational Policy, Dr. William S. Middleton, Chairman.

Dr. Middleton reported that his Committee had received a panel relative to the succession of representatives of the American College of Physicians on the American Board of Internal Medicine, and the Committee had recommended the reappointment of Dr. Alex. M. Burgess and Dr. Truman G. Schnabel for terms of three years, to 1951, and the nomination of three individuals, one of whom shall be selected by the American Board of Internal Medicine to fill the unexpired term of Dr. William S. McCann, resigned, until 1950.

. . The recommendations and nominations presented by Dr. Middleton's Committee were approved by resolution, and later Dr. Chester M. Jones was selected from the three nominees presented to succeed Dr. William S. McCann. . . .

DR. MORGAN: Next is the report from the Conference Committee on Graduate Training in Medicine, Dr. Reginald Fitz, Chairman.

DR. REGINALD FITZ: Dr. McCann has already said about everything the Committee has to say. Our Committee hopes to get the Council on Medical Education and Hospitals of the American Medical Association to hold a conference just before the annual meeting of the American Medical Association, and in that manner we hope that through the Council, the American Board and the College something more can be done than has been done heretofore.

DR. MORGAN: Next is the report from the Committee on the ANNALS OF INTERNAL MEDICINE, Dr. Francis G. Blake, Chairman.

DR. FRANCIS G. BLAKE: We have no report.

DR. MORGAN: May we have a report from the Editor of the ANNALS OF INTERNAL MEDICINE, Dr. Maurice C. Pincoffs?

DR. PINCOFFS: I received a communication from the Executive Secretary concerning the appointment of an Associate Editor in place of Dr. Gerald B. Webb, deceased, telling me that the Editor has the privilege of nominating a candidate to the Board of Regents. I should like to nominate Dr. James J. Waring to fill this vacancy.

. . . On motion by Dr. Walter L. Palmer, seconded by Dr. Alex. M. Burgess, and regularly carried, Dr. James J. Waring was appointed an Associate Editor. . . .

DR. PINCOFFS (continuing): I am glad to report that progress has been made in getting the ANNALS OF INTERNAL MEDICINE out on time, and that the circulation of the journal shows a most gratifying increase. At the present time we are printing 11,750 copies per month.

DR. MORGAN: That is an extraordinary figure for a journal in a special field.

May we now have the report of the Committee on Public Relations, Dr. James E. Paullin, Acting Chairman.

DR. PAULLIN: The Committee on Public Relations met at the Civic Auditorium, San Francisco, Calif., April 19, 1948, at 11:30 a.m.

I. Communications:

(1) A communication from Dr. Edward M. Hayden, Tucson, Ariz., concerning the rebating from lay and professional laboratories to physicians in Tucson and Phoenix, Ariz., for services rendered by clinical laboratories and roentgenological and pathological laboratories.

The Committee wishes to advise Dr. Hayden that the problem which he presents should be handled at a local level by his county medical society.

The American College of Physicians is unalterably opposed to any practice of rebating fees or any other procedure which is contrary to the principles of medical ethics established by the American Medical Association, or any practice in conflict to the Hippocratic Oath.

It is advised that if Dr. Hayden finds that any member of the American College of Physicians participates in either the rebating or splitting of fees in his own community, if he will prefer charges against such member directly to the Board of Regents, that we will investigate such charges and either discipline or expel any member for conduct which in the opinion of the Board of Regents is derogatory to the dignity of the College or inconsistent with its purposes.

. . . On motion by Dr. James E. Paullin, seconded by Dr. LeRoy H. Sloan, and regularly carried, the above recommendation was adopted. . . .

DR. PAULLIN (continuing):

(2) A communication from the American Association of Blood Banks requesting that the American College of Physicians approve their Constitution, a copy of which was enclosed, and that we endorse the purposes of their Association.

The Committee wishes to comment as follows: the consideration of such a request by the American Association of Blood Banks is beyond the scope and the purpose of the American College of Physicians. It is believed that the humanitarian program established by the American Red Cross fulfills all requirements of blood collection and distribution on a national level. This program has been endorsed by all national medical, dental, hospital and nursing organizations. It, to our mind, fulfills a national need. It does not in any way preclude the development of voluntary local programs.

(3) A communication from the California Society of Internal Medicine re a resolution passed by the Council of the California Society of Internal Medicine, relating to the National Red Cross Blood Bank Program, in which the conduct of such a program is criticized as an infringement on free enterprise and that the Council disapproves such activity by the National Red Cross.

Your Committee believes that since the national blood donor program has received endorsement of the American Medical Association, the American Dental Association, the American Pharmaceutical Association, the American Hospital Association, the American Nurses Association, and all other humanitarian organizations, and since it does not in any manner preclude the development of local voluntary programs, we disagree with the sentiments expressed by the California Society of Internal Medicine.

. . . On motion by Dr. James E. Paullin, seconded by Dr. Francis G. Blake, and regularly carried, the above recommendation was adopted. . . .

DR. PAULLIN (continuing):

(4) A communication from Dr. Edwin P. Jordan, of the Cleveland Clinic, to the Board of Regents, asking for information concerning the initiation fees and dues of members of that Clinic, in respect to their full-time participation in the Cleveland Clinic.

The Committee on Public Relations believes that the salary scale of the Cleveland Clinic is such that all members of the College connected with this and similar group organizations should be subject to the same initiation fee and dues as other members of the College in private practice. Since the Cleveland Clinic is operated on a non-profit basis and its surplus funds are devoted to postgraduate medical activities, it is suggested that in the event the initiation fee and dues should be a burden on any member of that Clinic, that the Foundation might give due consideration to defraying this expense, rather than the College giving a reduction of dues.

. . . On motion by Dr. James E. Paullin, seconded and regularly carried, the above recommendation was approved. . . .

DR. PAULLIN (continuing):

(5) It is believed that since the compensation of members of the Armed Forces (Navy, Army, Public Health Service and Veterans Adminis-

tration) has been increased and since in many instances income from these positions is more than that of many members of the College engaged in private practice that an investigation should be made by a committee relative to a revision of the reduction in initiation fee and dues previously granted to members of these services.

. . . On motion by Dr. James E. Paullin, seconded by Dr. Maurice C. Pincoffs, and regularly carried, the above recommendation was approved, with the provision that the Committee on Public Relations, with the help of Mr. Pindar, make the survey. . . .

DR. PAULLIN (continuing):

II. Resignations:

(1) *Dr. Reuben Hoffman (Associate), Henryton, Md.*
We recommend the acceptance of the above resignation.
(2) *Dr. Arnold McNitt (Associate), Washington, D. C.*
We recommend the acceptance of the above resignation.
(3) *Dr. J. Harold Root, F.A.C.P., Waterbury, Conn.*
We recommend the acceptance of the above resignation.
(4) *Dr. H. Andrew Wallhauser, F.A.C.P., Wittman, Md.*
It is recommended that the resignation of Dr. Wallhauser be not accepted, but that his dues be remitted until he is able to resume the practice of medicine.

. . . On motion by Dr. James E. Paullin, seconded by Dr. Maurice C. Pincoffs, and regularly carried, the recommendations concerning resignations were approved. . . .

DR. PAULLIN (continuing):

III. Fees and Dues Cases:

. . . Two cases were presented, one of a physician elected to Fellowship in the College in 1942, who six months thereafter entered military service but never completed taking up membership by the payment of the initiation fee of $30.00. The Committee felt that consequently up to this time this man is not a member of the American College of Physicians, and suggested that the Executive Secretary inform him that because he has never paid his original initiation fee, he has never qualified for Fellowship in the College, and that should he desire to become a Fellow, he must pay the fee. Should he do this, the Committee would recommend that there be a waiver of dues extended to him for the years 1947 and 1948, because of ill health, and until he is able to resume the practice of medicine.

. . . The second case was of a Fellow for whom the Committee recommended the waiver of dues, beginning January 1, 1948, because of physical disability and retirement from practice.

. . . On motion by Dr. James E. Paullin, seconded and regularly carried, both recommendations were approved. . . .

. . . Continuing his report, Dr. Paullin presented the case of one Fellow who is more than two years delinquent in dues, and, therefore, subject to being dropped automatically from the Roster, in accordance with provisions of the By-Laws.

. . . On motion by Dr. James E. Paullin, seconded by Dr. David P. Barr, the report of the Committee on Public Relations was approved as a whole. . . .

DR. MORGAN: Next item on the agenda is the report of the Committee on Finance, Dr. Charles F. Tenney, Chairman.

DR. CHARLES F. TENNEY: The full Committee on Finance met on Monday, April 19, and reviewed all financial matters at this time before the College.

A. . . . Dr. Tenney proceeded to present a recommendation from the Committee that the retirement annuity of the Executive Secretary be increased, discussed the cost and stated that the Executive Secretary himself, under the College retirement plan, would have to contribute 20% of the cost. Numerous questions were asked by various members of the Board, including the amount of the present annuity, whether the Finance Committee had gone into all details, what happens if the annuitant's services terminate, by death or disability, etc. The Committee did not have immediately available all of the information suggested, and a resolution was adopted referring the matter back to the Finance Committee for further study and for a detailed report at the next meeting of the Board of Regents. . . .

DR. TENNEY (continuing):

B. Auditor's Report for 1947:

The Auditor's Report has been carefully examined, accepted and approved by the Finance Committee, and copies thereof have been prepared and are now being placed in your hands.

(1) Salient Data:

(a) All accounts fully audited by Certified Public Accountant.
(b) Increase in Funds:

	Balance Jan 1, 1947	*Increase (Net)*	*Balance Dec. 31, 1947*
General Fund	$234,159.26	$36,411.56	$270,570.82
Endowment Fund ...	223,373.89	35,411.00	258,784.89
Bruce Fund	10,000.00		10,000.00
Brower Fund		2,500.00	2,500.00
	$467,533.15	$74,322.56	$541,855.71

(c) Gross Assets of the College—$631,641.75.
(d) On the Balance Sheet for 1947 operations, appears a balance of $94.60, "Building Alterations Fund," which was established in 1946 for a certain third-floor improvement. That is a separate and distinct fund from the Building Fund, and since it has not been used to date, it may be applied in part against the deficit of $153.88 of the Building Fund.
(e) The Balance Sheet discloses two restricted current funds:

Chicago Postgraduate Fund	$ 443.30
Philadelphia Postgraduate Fund	2,284.30

It was agreed by the Finance Committee that funds accumulated by the College from the Chicago Postgraduate Fund of $443.30 and by the Philadelphia Postgraduate Fund of $2,284.30, representing balances returned by directors of former courses, be closed out through the general accounts of the College and deposited in the current postgraduate account for use, inasmuch as they serve no practical purpose as restricted funds.
(f) Endowment Fund data:

Life Membership Fees, 1947, amounted to	$ 28,386.67
Profit on Investments	16.00
Donation, Dr. A. Blaine Brower	2,500.00

(g) General Fund data:

Total Income	$194,667.35
Total Expenses	151,139.01
Balance	$ 43,528.34

In 1946 the balance was $13,985.91. The net income for 1947 was nearly $29,000.00 more than anticipated when budgets were prepared in the autumn of 1946, and the expenditures were $15,000.00 less than budget provisions, exclusive entirely of the building program.

(h) Detailed financial statements disclose all details and give a certified registry of all investments.

C. Investment Counselor's Report and Recommendations:

(1) Analysis, as of March 29, 1948 (excluding A. Blaine Brower Fund):

	Endowment Fund	*General Fund*	*Total*
Market Value	$280,631.25	$178,175.00	$458,806.25
Book Value	266,788.11	156,076.42	422,864.53
Appreciation			$ 35,941.72

Current average yield, 4.01%.

(2) Additional purchases of securities (Endowment Fund) since last meeting of the Board of Regents:

12–3–47	80 Shares, General Electric Co., common	$2,846.49
3–29–48	2,500 U. S. of America Savings Bonds, Series "G", 2½s, 3–1–60	2,500.00 *
		$5,346.49

In accordance with regulations of the Board of Regents, the Committee requests approval of the above purchases, and I so move.

. . . The motion was seconded by William D. Stroud, and regularly carried. . . .

DR. TENNEY (continuing):

As a matter of record, the Committee reports the purchase of the following securities for the General Fund:

12–3–47	20 Shares, E. I. du Pont, common	$3,742.74
12–3–47	5,000 New York, New Haven & Hartford R.R. Co., Harlem River & Port Chester, First, 4s, due 1954	4,912.50
12–3–47	20 Shares, Phillips Petroleum Co.	980.00
		$9,635.24

(3) The Finance Committee approves of the following recommendations of Drexel & Co. for sales and purchases of the following securities:

* A. Blaine Brower Fund.

(a) *Sell*—General Fund:

30 Shares, American Telephone and Telegraph Co., Capital Stock

Purchase—General Fund:

130 Shares, American Gas and Electric Co., common

(b) Additional Investments:

Purchase—Endowment Fund:

5,000 Carolina, Clinchfield & Ohio Ry. Co., 1st "A", 4s, 9–1–65
4,000 Public Service Corp. of New Jersey, Perpetual, 6s
5,000 Philadelphia Co., Coll. Tr., 4¼s, 7–1–61
4,000 American Tobacco Co., Deb., 3s, 10–15–69

Purchase—General Fund:

60 Shares, Continental Insurance Co.
100 Shares, Chrysler Corp.
50 Shares, Timken Roller Bearing Co.
25 Shares, Union Carbide & Carbon Corp.
80 Shares, Phillips Petroleum Co.

The Committee asks specifically the approval of the above transactions which affect the Endowment Fund, and I so move.

. . . The motion was seconded by William D. Stroud, and regularly carried. . . .

DR. TENNEY (continuing):

The Finance Committee has agreed to consult the Investment Counselor concerning the possibility of reducing from 31 to 25 per cent the present holdings of the College in Government Bonds. That is, at the present time 31 per cent of our investments are in Government Bonds, whereas the Committee desires further analysis by Drexel & Co. of the desirability of possibly reducing the proportion of Government Bonds in our portfolio from 31 to 25 per cent.

DR. MORGAN: It is the sense of this Board that it is the function of the Finance Committee, and we will entertain any recommendation relative to this problem, after you have made the study.

DR. TENNEY (continuing):

D. General Comments:

The dues were increased (returned to the original rates) on January 1, 1947, and most of our members who served during the War returned to civilian status and, thus, resumed payment of dues during 1947. This, with some additions to membership, accounts for the following comparisons:

	1946	*1947*
Annual Dues	$32,806.61	$53,516.25
Initiation Fees	12,660.00	15,538.67
ANNALS, Subscriptions	50,625.30	62,435.59

Life Membership Fees are still keeping up, though not in excess of 1946:

	1946	*1947*
Life Membership Fees received	$28,495.15	28,386.67

Annual Sessions, 1946 and 1947:

At the 1946 Annual Session there was a surplus of income over expenses of $5,203.50.

At the 1947 Annual Session, there was a deficit of $5,135.85, largely due to greatly increased expenses at Chicago over Philadelphia, partially arising from rental of exhibit space and increase of more than $1,000.00 for the President's expenses and generally increased costs.

ANNALS OF INTERNAL MEDICINE comparison of the years 1946 and 1947 are as follows:

	1946	*1947*
Subscriptions	$50,625.30	$62,435.59
Advertising	23,661.69	26,246.07
	$74,286.99	$88,681.66
Expenses	46,140.47	57,319.32
Net Profit	$28,146.52	$31,362.34

It is to be pointed out that the printing costs for the ANNALS is steadily and sharply rising, the comparison between 1946 and 1947 being $31,179.00 for 1946; $38,054.00 for 1947. Furthermore, there will be further increased basic printing costs in 1948 over 1947, because the last printer's increase became effective only on August 1, 1947. Additionally the Editor is now gradually increasing the size of the ANNALS, which will add materially to the cost.

. . . On motion by Dr. George F. Strong, seconded by Dr. Reginald Fitz, and regularly carried, the report of the Finance Committee was accepted as a whole. . . .

DR. MORGAN: Next is a communication from Dr. William S. Middleton.

DR. MIDDLETON: Mr. Chairman, the Committee on Educational Policy has under advisement a matter of serious importances to all of us, and I believe that the medical profession of the country looks to the American College of Physicians for guidance, for leadership in educational and research fields. With the present growth and knowledge of, and the prospect of an expansion in the application of, radioactive and stable isotopes, the Committee on Educational Policy feels there should be an active part played by this College. Therefore, it is recommended that research fellowships in the study of radioactive and stable isotopes in the field of biology and medicine be named and supported by the College in numbers not to exceed five. I move the acceptance of that recommendation.

DR. MORGAN: That would mean an expenditure of some ten or fifteen thousand dollars additional on research fellowships.

DR. TENNEY: I second the motion.

DR. PINCOFFS: I rise on a point of information. Has it been considered by the Committee how many opportunities with pay there already are for men who wish to go into this field? I am under the impression that there is a very generous allotment of Government funds covering many aspects in this field. Opportunities to go from paid positions in universities, or otherwise to carry on work for shorter or longer periods of time through fellowship or sundry other ways for which public funds are available, are far greater than the number of physicians who wish to enter this work. I may not be entirely accurate about this, however, and I should like to have information on it that would directly bear on whether we wish to expend College funds.

DR. MIDDLETON: There are two positions to be taken—first, opportunities do exist. These opportunities do not encompass the entire field, and there are vacancies currently that could be filled, were other funds available. That is the material aspect of it. The second aspect is from the standpoint of medical leadership; in these times with the incalculable range of application of these new skills, I believe the American College of Physicians would be remiss in not accepting this responsibility, and failing to enter this field specifically. That is to say, not in expansive terms, if there were not more than two places available, certainly we would not attempt to place five fellows. A maximum of five and certainly two or three such fellowships would be bread on the water.

DR. PAULLIN: I think all of us are in sympathy with Dr. Middleton's suggestion, but we have a Finance Committee that is requested to look after these expenditures, and when we recommend an appropriation of money, we are not quite certain our budget can withstand it. While I am quite sympathetic with this idea, at the same time I think it should be accepted in principle, subject to review by the Finance Committee, as to whether we can spend that much money. Our expenses in the College are getting terrible. This Annual Meeting here is going to be the most expensive we have ever had. We should look at our purse before we spend too much money.

DR. DAVID P. BARR: I was unable to take part in the discussions of this Committee on Educational Policy on this particular subject. I am sure that the importance of this method of study cannot be exaggerated, and I can see a certain advantage in the College taking the position of recognizing the need for such work. However, I have the feeling that almost every field of investigation is going to be permeated with the use of isotopes, including most of our regular research fellows. There is a question as to whether it is appropriate to separate those fellowships which have to do with the use of isotopes and those that have to do with medical research in general.

I happen to know something about the provisions which are being made for study by the Atomic Energy Commission—and other agencies—for this type of work. I have the feeling, as to our own institution, that just as fast as the young men are ready to engage in this field, they will find unusual and ample opportunities for support from the Atomic Energy Commission. That, as Dr. Pincoffs pointed out, would be not only for the use of the Governmental laboratories in different parts of the country, but also for fellowship salaries. I do not believe I would be in a position to concur in this recommendation.

DR. FITZ: My mind reacts as did Dr. Barr's. I think it is a great mistake, from the point of view of fellowship policy, to separate the funds. I would much rather have the fellowships set up as they are now, and if a man came along who was properly qualified and wished to work in this field, grant him one of our ordinary fellowships. I think it would prove narrow-minded, in the long run, to specify exactly what kind of work one of our fellows should enter.

. . . The Chair at this point, forgetting that the motion had already been seconded, inquired if any one would second the original motion. There was no such second, and the Chair declared the motion failed for lack thereof. . . .

DR. MORGAN: I think, Dr. Middleton, certainly our experience during this next year, the experience of the Committee on Fellowships and Awards, will be useful, and I think we might well reintroduce such a motion at our next meeting, if applications this year indicate the demand over and above that which we can meet with our regular appropriated funds for fellowships.

We must now consider the recommendation made by the Committee on Credentials at the November, 1947, meeting, embodying two recommendations. The first was the Committee realizes that the number of applicants for admission is growing steadily. The question comes up from time to time about a candidate who is not an internist, but is a neuropsychiatrist, a dermatologist, or some other affiliated specialist. The informative booklet of the College says that membership need not be made up only of internists, but may include those properly qualified in pediatrics, neurology,

psychiatry, public health, radiology, and so forth. The Committee believes it would be well seriously to consider changing our regulations and limiting membership to those who are internists, and to discontinue, after a certain time, to take in men who are not internists, even though they be engaged in affiliated specialties.

This would exclude determatologists, pediatricians, and a few others.

The second has to do with requiring certification by the American Board of Internal Medicine, or an allied Board, such as the American Board of Pathology, before a candidate is eligible for Associateship.

I suggest that the Board of Regents take action on these two matters at this meeting, because of the increasing size of the College and the inevitable limit in the size of the College, membership shall be limited to those who are internists and we shall not accept men, even though they are qualified by their respective boards, in dermatology, neuropsychiatry or radiology. Do I hear a discussion relative to this proposal from the Committee on Credentials?

DR. ALEX. M. BURGESS: Will you further elaborate on the affiliated specialties that would be excluded? You mention dermatology, pediatrics, neuropsychiatry, and, I recall in some previous discussion, something was said about not excluding pathologists and clinical pathologists.

DR. PINCOFFS: I make a motion that the American College of Physicians shall not accept as qualifications for membership certification by the American Boards of Dermatology, of Pediatrics, of Neurology and Psychiatry, and of Radiology.

DR. A. B. BROWER: I second the motion.

DR. WALTER L. PALMER: I rise to question what is the proper procedure in the College. On Sunday afternoon this was discussed with the Regents and the Governors. Last year a similar question was discussed with the Governors. Where do the Governors come in, or where should we come in on these questions?

Now it seems to me if the Regents want to act on these questions without consulting the Governors, if that is the policy of the College, it is all right, but on the other hand, if they do wish to consult the Governors on these two questions, then I think they should give the Governors an opportunity to discuss those two questions and make a recommendation to the Regents. Of course, if you did that, the Regents might be confronted with the situation of wanting to overrule the Governors. I think procedure-wise it would be better to let the Governors discuss this first.

DR. MORGAN: Your point is well taken.

DR. GEORGE MORRIS PIERSOL: It is on their agenda. They have the question of whether these matters will involve a revision of the Constitution and By-Laws. The proper way might be to have it handed over to the Committee on Constitution and By-Laws and invent the machinery for it. All we can do today would be to pass a motion in which we recommend the modification of the By-Laws, which will require another year at least to put into effect. In the meantime, the Governors have the same problem. The Committee on Constitution and By-Laws would have to be governed by the joint action of these two bodies.

DR. BROWER: I would like to move that you lay this motion on the table, until after the meeting of the Board of Governors tomorrow.

DR. PAULLIN: I second the motion.

. . . The previous motion was withdrawn, the new motion put to vote and carried. . . .

DR. MORGAN: I think the Chair will rule that the second point belongs in the same category and will not be acted upon until the Governors have had a chance to discuss it further.

DR. PIERSOL: I feel strongly that the ideas of the Governors should be solicited on these points. I might say, in connection with the second one, since that recommendation was made, members of our own Committee have been very definite in their suggestions that perhaps another way out of the difficulty would be to increase the age limit for admission to Associateship; another suggestion was that it might

be well to increase the period of Associateship during which a man may qualify for Fellowship. Both of these would to some extent solve the difficulty. Then a final suggestion was made to me by some distinguished members of this Board—it is shocking, but in the end it is what will have to happen and will happen—and that is that we cut the Gordian knot and abolish Associateship, and merely have requirements for admission to Fellowship, based on whatever requirements or qualifications, which obviously will include certification, the Board of Regents may specify.

Several distinguished bodies have had groups of Associates and within the last few years have come to the conclusion that it is unsatisfactory and cumbersome, and that the best plan is to wait until a man is qualified for admission wholly into the organization as a Fellow. This idea has merit, and, in the long run, I personally believe it will add to the dignity of this group. I am firmly convinced that the day is not too far off when that will be the solution of our problem.

DR. MORGAN: With your permission, Dr. Piersol, we shall then defer action at this meeting on the second item. This certainly has to do with the most important functions of the administration of this College, and I know that your insistence upon action stems from difficulties you have had.

I wonder what you think of this suggestion—that after the Board of Governors consider these two matters tomorrow, that you convene your Committee on Credentials together with the Executive Committee of the Regents a day early in the autumn and spend the entire day going over this matter, with the hope that out of such a meeting would come solid recommendations which the Board of Regents could act upon? I offer it as a suggestion for the incoming administration.

DR. PIERSOL: That is a good suggestion.

DR. GEORGE F. STRONG: I would like to elaborate further on what Dr. Palmer said. I served on the Board of Governors, and I know the feeling of inadequacy or ineffectiveness of that group is very real. It seems to me that as a matter of policy, and in the best interests of the College, it would be wise if there was a division of responsibility in this matter. It is the Governors essentially who pass on the names that are proposed for Associateship and Fellowship. It is the function of the Governors to consider what the requirement for those Associates and Fellows should be. We should delegate matters having to do with requirements and qualifications to the Governors, and give them a sense of responsibility.

. . . Dr. James E. Paullin arose to speak personally to the Regents at this time, marking his last day's membership on the Board of Regents, after many years of service, but at his own request his comments were not recorded. . . .

DR. MORGAN: Dr. Paullin, I join the group in a rising vote of abiding affection. (Applause.) The meeting is adjourned.

. . . Adjournment, 3:15 p.m. . . .

Attest: E. R. LOVELAND,
Executive Secretary

ANNUAL BUSINESS MEETING

SAN FRANCISCO, CALIF.

APRIL 22, 1948

The Annual Business Meeting of the American College of Physicians was called to order at the Civic Auditorium, San Francisco, Calif., April 22, 1948, at 2:00 p.m., with President Hugh J. Morgan presiding, and with Mr. E. R. Loveland acting as Secretary.

PRESIDENT HUGH J. MORGAN: I declare that there is a quorum present and that the Annual Business Meeting is in order. The Secretary, Mr. E. R. Loveland, will read the abstract of the Minutes of the preceding Annual Business Meeting.

. . . Mr. E. R. Loveland read the abstract of the Minutes, which by resolution was approved as read. . . .

PRESIDENT MORGAN: We shall have the annual report of the Treasurer, Dr. William D. Stroud.

DR. WILLIAM D. STROUD: Mr. President, Fellows and Masters of the College—The details of all operations of the College for 1947, along with the certified public accountant's audit, will be published to the members through the ANNALS OF INTERNAL MEDICINE. During the year 1947 the College added to its General Fund $36,411.56, to its Endowment Fund $35,411.00, and received a gift in trust of $2,500.00, an initial deposit on an educational trust fund of $10,000.00 subscribed by one of our Fellows, Dr. A. B. Brower. The gross assets of the College, as of December 31, 1947, amounted to $631,641.75—$270,570.00 is in the General Fund and $271,284.00 is in the Endowment Fund, and the balance represents real estate, furniture and equipment.

The College operated entirely within its budget for the year. Its investments are carefully watched by our Investment Counselor and the Committee on Finance, and our investment accounts are in a favorable condition. As of December 31, 1947, the College held investments at book value totalling:

Endowment Fund	$266,788.11
General Fund	156,076.42
	$422,864.53

The current market value of these securities is $458,806.25, showing an appreciation of $35,941.72. The current average yield on our securities is 4 per cent.

The Board of Regents has approved a budget for 1948 calling for an estimated income of approximately $194,000.00, and an estimated expenditure of approximately $153,000.00, leaving an anticipated balance of $41,000.00. The financial policies of the College are directed along conservative lines.

. . . On motion made, duly seconded and carried, the report of the Treasurer was accepted. . . .

PRESIDENT MORGAN: Next is the report of the Executive Secretary, Mr. E. R. Loveland.

MR. E. R. LOVELAND: Mr. President, Fellows and Masters: My report is supplementary to those of the Treasurer, the Secretary-General and the President. During the recent war 35 per cent of our members were in the Armed Forces; they have practically all returned to civilian activities and their resumption of active membership.

There has been a marked increase in the interest of younger physicians who are aspiring to membership in the College, and this will be reflected in a materially growing number of candidates for Associateship.

During 1947 there was a continued increase in the volume of College activities. The circulation of the ANNALS OF INTERNAL MEDICINE grew 15 per cent, this increase coming not only from physicians in the United States but from other countries throughout the world. The circulation is now over 11,600 copies per month.

Since the last Annual Session of the College, we have conducted twenty-one formal Regional Meetings, largely of the single State character, but in some instances of the multi-State character. These meetings are of a more intimate type than the Annual Session; they give an opportunity for closer acquaintanceship in each Governor's territory, present an opportunity for younger members to present papers and, in many instances, for the local members to meet and observe younger physicians who are being proposed for Associateship.

Due to labor conditions and a continued shortage of paper, we have not been able to republish the complete Directory of the College, but have, by direction of the Board of Regents, substituted Membership Rosters. A new Membership Roster for 1948

is in process of publication, and will be ready for distribution in the late summer. Those who have not returned the data forms for the new Roster are requested to do so without further delay.

For the last few years the College Building in Philadelphia has been inadequate in size for the growing activities and increased staff. One year ago your Board of Regents, through the House Committee, authorized an addition to the building, which was begun during September and is now completed, which provides us with superb working facilities and is an addition of which the College is justly proud. Our members again are cordially invited to visit the College offices whenever they are in Philadelphia. Your Executive Secretary and his staff are deeply gratified with the cordial relations and the oft expressed appreciation of its work by the members at large, which is a constant stimulation to greater effort and an increased desire to serve them more efficiently in all ways possible.

I have just received from the Registration Desk a report that the total registration at this moment is 3,083, of which 487 are ladies.

PRESIDENT MORGAN: May I suggest a rising vote of appreciation and thanks to Mr. Loveland?

. . . Rising vote of approval and thanks to Mr. Loveland. . . .

PRESIDENT MORGAN: And may I add that Mr. Loveland is an educational and business administrator extraordinary.

The next item on the agenda is the annual report of the Secretary-General, Dr. George Morris Piersol.

DR. GEORGE MORRIS PIERSOL: Mr. President, Officers, Regents, Governors, Masters and Fellows of the College:

Membership: Since the last Annual Session of the College, there have been elected 5 Masters, 211 Fellows, and 388 Associates, which brings the total membership to 6,250, divided as follows:

11	Masters
4,567	Fellows
1,672	Associates
6,250	TOTAL

Life Members: During the past year 96 Fellows have become Life Members of the College, bringing the total to 708, of whom 51 are deceased, leaving a balance of 657.

Deaths: It is with regret that we report the deaths of 2 Masters, 80 Fellows and 5 Associates during this period. Their names and records have been recorded in the archives of the College.

Postgraduate Courses: The Advisory Committee on Postgraduate Courses has continued its activities, in many cases expanding our courses to new fields. Through their efforts there were organized 21 separate and distinct courses during 1947, and there are 9 courses on the spring program of 1948. There is a very satisfactory registration for all of the current courses. Approximately one thousand doctors attend the College courses each year, evidencing the popularity and value of this feature of the College activities.

Fellowships: A further important educational activity of the College has been the creation and extension of Research Fellowships. Approximately $20,000.00 per annum is allocated to these fellowships. Seven new fellowships have been awarded to begin on July 1, 1948.

As gratifying as are the above mentioned educational activities of the College, it should not be overlooked that the most significant and far-reaching contribution of the College is its Annual Session. These have been marked by progressively improved

programs and ever widening scope. The current session is a further outstanding example of what may be accomplished by a year's well coördinated effort. The College is mindful of its great debt to those who have made this San Francisco Session possible.

. . . . . .

Now, Mr. President, throughout this past year, as President of the American College of Physicians, you have guided the destiny of this organization and you have carried out its purposes with good judgment and exceptional ability. Those of us whose privilege it has been to be closely associated with you in the conduct of the College are keenly aware of the never failing courtesy, forebearance and coöperation that have marked your every act. Therefore, it is our desire to express to you in some enduring way our appreciation and affection, and so, on behalf of your fellow Officers, the Regents and Governors of the American College of Physicians, it is our pleasure to present to you this gavel. (Applause.)

PRESIDENT MORGAN: Dr. Piersol, thank you and through you the Officers, Regents and Governors and Fellows of this College. This gavel constitutes a souvenir of the most important and I hope most useful year of my life.

It is now my great pleasure to present to you our new President. I first knew him when he came to Baltimore from active duty with the Medical Department of the Army after World War I to help Dr. Sydney Thayer, Professor of Medicine, organize the Department of Medicine. He not only taught Clinical Medicine at Johns Hopkins with Dr. Thayer, but he also developed there an extraordinary laboratory for clinical investigation in the biochemistry of metabolic diseases.

He has degrees from Amherst, Harvard and Columbia, and at one time or another has worked at the Massachusetts General Hospital, the Hospital of the Rockefeller Institute, the Johns Hopkins Hospital of Baltimore and the Presbyterian Hospital in New York. He was the Bard Professor of Medicine at Columbia until he retired to assume his present position as Director of the Public Health Research Institute of the City of New York.

It is an honor to present to you the President of the College, Dr. Walter W. Palmer. (Applause.)

. . . Dr. Walter W. Palmer assumed the Chair. . . .

PRESIDENT WALTER W. PALMER: Members of the College, I wish to express my keen and sincere appreciation of the honor which you have conferred. I assume the duty as President of this distinguished College with a great deal of trepidation. I am following a man who has set a precedent that is going to be impossible to excel and most difficult to equal.

We have had here in San Francisco an unusual and an extremely gratifying experience. It is, I think, the best meeting I have ever attended. That is a great inspiration for us who will try to put on an Annual Session next year in New York.

I shall attempt to outline the future policies. We are living in a time when future policies and plans are likely to be interrupted. It is not easy to make long term plans with the world and this country in the present situation. One has only to glance at our newspapers, or listen to the radio; on the whole, it is most depressing. However, as physicians, we should not be drepressed, but should do our duty. Mainly, we shall have to change this year, or the next, or some time in the future, from the business that we love to more urgent and pressing duties.

Certainly with the extraordinarily well organized committees, headed by our remarkable Executive Secretary, the American College can go on without any interruption. The wonderful educational program which has been developed over the past—the Regional Meetings, the Postgraduate Courses—should be as good or better than in the past. The first activities have not been extensive, but they have been valuable and important. All of you have attended these Regional Meetings, programs

and dinners, and you will realize, I am sure, how important the progress of medicine is and how dependent on research in the basic sciences.

We are all aware of the fact that there are now enormous sums devoted to the study of cancer—millions for cancer, millions for poliomyelitis, and large sums for the study of the diseases of old age. These sums are drawing into the field large numbers of investigators, and they are going to announce the results of their investigations, and the duty falls upon this College to try to get these results before its members as rapidly and in as good form as possible. This will be one of our duties next year, and a more important duty, perhaps, than before, because the numbers are greater, they are working longer and we may expect more results than in the past.

There is a feature of this development in this country that has a sobering effect upon men who are interested in investigation. Of the money given for specific purposes, as indicated by what I have said, there is a very important division in the field of the sciences which is having a harder time in spite of all the money now available. This is the man who is finding his haven in the university engaged in the basic materials, not on any project that is handed to him, but he is following his own fancy, the dictates of his own interest. Such a man has to depend upon university funds to a large extent—the small budget developed by the university for teaching. Universities are having a hard time, despite the money available for these things, and something is necessary, in order to relieve their anxiety. The money that used to go to the universities now goes into the tax pots. We must, I feel, look to tax money to help us out in research in the basic fields.

It was my privilege to serve on the medical committee with Dr. Vannevar Bush, who, at the request of President Roosevelt, made that very interesting and valuable report to President Truman on the need for a National Research Foundation to supply the need, the support for basic science work. This report, after batting about in Congress for a couple of years, finally was passed last year but vetoed by President Truman, because it didn't conform to certain Government precedents in the matter of organization.

I believe that this matter is so important that the obstacles presented in it—and I may say, based upon Dr. Vannevar Bush's report—will be removed, and we shall have a National Science Foundation which will support the men whom I consider so very important. I think they are the most important in our progress, not only in medicine, but in science in general. Thank you! (Applause.)

* * *

We shall proceed with our agenda and ask the Secretary to present an amendment to the Constitution, this amendment having already been approved by the Board of Regents, and is now subject to approval of the Fellows and Masters of the College.

MR. LOVELAND: The By-Laws of the College were amended last year at the Annual Session, and, among other things, there was provided a new Article VI for the election of Masters, in which it is specified "A special Committee on Masterships will be named by the President. . . ." It was overlooked at that time that in the Constitution, Article IV (b), a minor amendment should be made changing the wording from "Committee on Credentials" to "Committee on Masterships," which makes the revised paragraph read as follows:

> "(b) Masters. Masters of the American College of Physicians shall be those who have attained the rank of Fellows, and who on account of personal character, positions of influence and honor, eminence in practice or in medical research, or other attainments in science or in the art of medicine, are recommended by the Committee on Masterships to the Board of Regents for special and well-earned distinction. Such Masters shall be designated as Masters of the American College of Physicians, and shall be authorized to use the letters M.A.C.P. in connection with scientific publica-

tions, at professional and academic functions and in connection with their professional activities.

Masters shall have the right to vote and to hold office."

PRESIDENT PALMER: You have heard the recommendation for the amendment to the Constitution. What is your pleasure?

. . . A motion was made to approve the amendment. It was duly seconded, voted upon and carried. . . .

PRESIDENT PALMER: Next on the agenda is the report of the Committee on Nominations by its Chairman, Dr. William D. Stroud.

DR. WILLIAM D. STROUD: Mr. President, Officers, Fellows and Masters of the College: In accordance with the provisions of the Constitution and By-Laws, the Nominating Committee has placed in nomination and has published in the ANNALS OF INTERNAL MEDICINE the names of the nominees to the elective offices, and at this time will place in nomination the following names for the Board of Regents and Board of Governors. These nominations do not preclude nominations that may be made from the floor:

Elective Offices:

President-Elect ..... Dr. Reginald Fitz, Boston, Mass.
First Vice President ..... Dr. William S. Middleton, Madison, Wis.
Second Vice President ..... Dr. Maurice C. Pincoffs, Baltimore, Md.
Third Vice President ..... Dr. Charles E. Watts, Seattle, Wash.

PRESIDENT PALMER: You have heard the nominations for the elective offices of the College. Are there any nominations from the floor, and what is your pleasure?

. . . It was moved and seconded that the nominations for the Elective Offices be closed, and that the Secretary be instructed to cast the ballot for the election of the above nominees. . . .

DR. STROUD (continuing): The Nominating Committee places in nomination the following names as members of the Board of Regents, for term expiring 1951:

Dr. Hugh J. Morgan ..... Nashville, Tenn.
Dr. Walter B. Martin ..... Norfolk, Va.
Dr. LeRoy H. Sloan ..... Chicago, Ill.
Dr. George F. Strong ..... Vancouver, B. C., Canada
Dr. Marion A. Blankenhorn ..... Cincinnati, Ohio

PRESIDENT PALMER: You have heard the nominations for the Board of Regents. Are there any nominations from the floor, and what is your pleasure?

. . . It was moved and seconded that nominations for the Board of Regents be closed, and that the Secretary cast the ballot for the election of the nominees above named. The motion was voted and carried. . . .

DR. STROUD (continuing): The Nominating Committee places in nomination the following names for the Board of Governors, for term expiring 1951:

Dr. E. Dice Lineberry, Birmingham ..... ALABAMA
Dr. Leslie R. Kober, Phoenix ..... ARIZONA
Dr. Lemuel C. McGee, Wilmington ..... DELAWARE
Dr. William C. Blake, Tampa ..... FLORIDA
Dr. Carter Smith, Atlanta ..... GEORGIA
Dr. Samuel M. Poindexter, Boise ..... IDAHO
Dr. Walter L. Palmer, Chicago ..... ILLINOIS (Northern)
Dr. J. Murray Kinsman, Louisville ..... KENTUCKY
Dr. Richard S. Hawkes, Portland ..... MAINE
Dr. Wetherbee Fort, Baltimore ..... MARYLAND
Dr. John G. Archer, Greenville ..... MISSISSIPPI

Dr. Harold W. Gregg, Butte .....MONTANA and WYOMING
Dr. Robert O. Brown, Sante Fe .....NEW MEXICO
Dr. Asa L. Lincoln, New York .....NEW YORK (Eastern)
Dr. Charles A. Doan, Columbus .....OHIO
Dr. Howard P. Lewis, Portland .....OREGON
Dr. David W. Carter, Jr., Dallas .....TEXAS
Dr. Karver L. Puestow, Madison .....WISCONSIN
Dr. Rafael Rodriguez-Molina, San Juan ...PUERTO RICO
Dr. Charles H. A. Walton, Winnipeg .....MANITOBA and SASKATCHEWAN
Dr. John W. Scott, Edmonton .....ALBERTA and BRITISH COLUMBIA

PRESIDENT PALMER: You have heard the nominations for the Board of Governors. Are there any nominations from the floor, and what is your pleasure?

. . . It was moved and seconded that nominations for the Board of Governors be closed, and that the Secretary cast the ballot. The motion was voted and carried. . . .

PRESIDENT PALMER: It is now my pleasure to ask Dr. F. Gorham Brigham and Dr. Alex. M. Burgess to escort Dr. Reginald Fitz, the new President-Elect, to the platform.

It is a great pleasure to introduce Dr. Fitz, of Boston, as your President-Elect.

DR. REGINALD FITZ: Mr. President, Follows and Masters of this College, I am sure I feel just exactly as you all must feel who have been elected to office in this College. In electing me as your President-Elect, you have paid me one of the highest compliments that could possibly come to any doctor in this country in this day and age. All I can do in accepting this office is to pledge myself to carry forward the ideals and the work of the College during the next succeeding year. I thank you all for the honor you have given me. (Applause.)

PRESIDENT PALMER: I should like to announce that the 1949 Annual Session will be held in New York City, March 28–April 1.

Are there any resolutions to be presented?

DR. T. GRIER MILLER: Mr. President, Masters and Fellows of the College, I wish to present the following resolution of thanks, and to move that it be spread on the Minutes of this meeting:

"RESOLUTION OF THANKS to our distinguished leader and President, Dr. Hugh J. Morgan, for the inspiration of his guidance during the past year, as well as during this Annual Session; to his Chiefs of Staff, General Chairmen William J. Kerr and Ernest H. Falconer, for a magnificent program; to the Chairmen of their local Committees, Dr. Sidney J. Shipman, Chairman of the Committee on Entertainment; to Dr. Dwight L. Wilbur, Chairman of the Committee on Clinics; to Dr. George S. Johnson, Chairman of the Committee on Hotels and Transportation; to Dr. Roberto F. Escamilla, Chairman of the Committee on Panel Discussions; to Dr. William C. Voorsanger, Chairman of the Committee on Publicity, and to the individual members of each of those Committees;

To Mrs. Stacy R. Mettier, Chairman of the Ladies' Entertainment Committee, and to all of her worthy and capable colleagues, Mrs. Sidney J. Shipman, Mrs. Roberto F. Escamilla, Mrs. William J. Kerr, Mrs. Ernest H. Falconer, Mrs. J. C. Geiger, Mrs. Edward Matzger, Mrs. William C. Voorsanger, Mrs. Dwight L. Wilbur, and all the others who have so ably and graciously taken care of the visiting ladies;

To Mr. Daniel Wilkes of our Press Office and to the public press; to Mr. Walter G. Swanson, Vice President and General Manager of the San Francisco Convention and Tourist Bureau, and Dr. Harold G. Trimble of the Entertainment Committee who so kindly handled the distribution of the tickets for the Concert on Monday evening; to all of these and many others, individually and

collectively, our heartfelt thanks again for their generous hospitality in full measure—pressed down and running over."

PRESIDENT PALMER: I would like to see a rising expression of enthusiasm for this resolution, a standing vote.

. . . A rising vote of applause was given in favor of this resolution. . . .

PRESIDENT PALMER: If there is no other business to come before this meeting, I declare it adjourned.

Adjournment——2:45 p.m.

Attest: E. R. LOVELAND,
Executive Secretary

ABRIDGED MINUTES OF THE BOARD OF REGENTS

SAN FRANCISCO, CALIF.

APRIL 23, 1948

The concluding meeting of the Board of Regents, held during the 29th Annual Session at San Francisco, Calif., was called to order at 1:00 p.m. in Room 203 of the Civic Auditorium on April 23, 1948, with President Walter W. Palmer presiding, and Mr. E. R. Loveland acting as Secretary. Roll call revealed the following in attendance:

Walter W. Palmer, *President;* Reginald Fitz, *President-Elect;* Maurice C. Pincoffs, *Second Vice President;* T. Grier Miller, Charles F. Moffatt, Charles F. Tenney, A. B. Brower, Alex. M. Burgess, Ernest H. Falconer, Cyrus C. Sturgis, Walter B. Martin, Hugh J. Morgan, LeRoy H. Sloan, George F. Strong, Walter L. Palmer, *Chairman, Board of Governors.*

. . . Reading of the Minutes of the preceding meeting of the Board of Regents was dispensed with. . . .

PRESIDENT WALTER W. PALMER: We shall have the report of the Committee on Nursing, Dr. Francis G. Blake, Chairman.

Dr. Blake is unable to be here, and since I was present at the meeting, I shall read Dr. Blake's report:

"The Committee on Nursing Service held a meeting at New Haven, Conn., on Tuesday, March 30, 1948. Dr. Walter W. Palmer, Dr. Thomas P. Murdock and Dr. Francis G. Blake, Chairman, were present. An invitation had previously been extended individually to Dr. Howard C. Naffziger, Chairman, and to Dr. Harold L. Foss and Dr. Leland S. McKittrick, members of the corresponding Committee of the American College of Surgeons, to attend the meeting, but they were unable to be present.

"For the information of the Committee, Dr. Murdock, Chairman of the Committee on Nursing Problems of the American Medical Association, reviewed in detail the extensive studies of nursing which have been conducted by the A.M.A. Committee, and the facts, opinions and proposals derived from joint meetings and conferences of this Committee with leaders in the educational, administrative and public health fields of the nursing profession, representatives of the American Hospital Association, the American College of Surgeons, the American Nurses Association, and other interested and informed persons.

"As a result of these studies, the Committee of the American Medical Association has arrived at tentative conclusions concerning the requirements for nurses during the coming decade and is preparing a series of recommendations devised to solve current problems. It is expected that the report of this Committee will be completed and ready for presentation in June.

"The Committee of the College finds itself in general agreement with the tentative conclusions and proposed recommendations of the A.M.A. Committee, but feels that it would be inappropriate to report further on them at this time, prior to their publication. It also is of the opinion that the studies, conferences and recommendations reported to us by Dr. Murdock have been so comprehensive and valuable that little of significance could be added by the Committee of the College. It is, therefore, recommended that the Committee be discharged.

"Respectfully submitted,

Thomas P. Murdock
Walter W. Palmer
Francis G. Blake, Chairman"

What is your pleasure regarding this report?

. . . On motion by Dr. Hugh J. Morgan, seconded by Dr. Ernest H. Falconer, and regularly carried, the above report was adopted. . . .

. . . In accordance with regulations of the Constitution and By-Laws, and additional previous resolutions of the Board of Regents, Dr. George Morris Piersol was reëlected Secretary-General, Dr. William D. Stroud was reëlected Treasurer, and the various standing Committees were appointed. (The lists and personnel of these Committees have been published elsewhere and are not herein repeated.) . . .

. . . Dr. Franklin M. Hanger, Jr., of New York City, was appointed by the Board of Regents as the General Chairman for the 1949 Annual Session. . . .

. . . Inasmuch as there appeared no real occasion for the continuance of the Council for Study, Prevention and Treatment of Rheumatic Fever, that Council was discontinued. . . .

PRESIDENT PALMER: We shall proceed with the agenda. The next is the report from the Board of Governors, Dr. Walter L. Palmer, Chairman.

DR. WALTER L. PALMER: There are two items that came before the Board on Wednesday which may be of some interest to the Board of Regents. The first was the discussion and action on the motion that Dr. Edgar V. Allen introduced last year, as a result of which a Committee of Five was appointed to discuss the procedure governing the election of Governors, getting the sentiment of members in each district, and so forth. The net results of the discussion of some forty minutes by the Governors was that the Board voted about three to one to allow things to stand as they are.

The other item which received a great deal of discussion was the report of the Committee on Credentials, with regard to two special recommendations—one regarding the discontinuance of taking members outside of internal medicine. Dr. Alex. M. Burgess kindly consented to be present at the meeting of the Board of Governors as an Alternate for Rhode Island, and Dr. Wallace M. Yater, a member of our Credentials Committee, was there as the Governor for the District of Columbia. The Board finally voted, at least three to one, against the restriction of pediatricians, neuropsychiatrists, etc. In other words, the Board does not approve of the limiting of the College to those interested only in internal medicine.

Then with regard to the other recommendation of the Committee on Credentials, namely, that certification be a prerequisite for Associateship, there was a great deal of discussion, and again the Board voted against that recommendation. There was still another item of interest growing out of Dr. Chester S. Keefer making the suggestion that Associateship be eliminated altogether. Dr. Alex. M. Burgess supported that position, and finally, for the sake of getting some indication of sentiment among the Governors, a resolution was adopted that the present feeling of that Board was that Associateship should eventually be discontinued, and that resolution was supported almost three to one, although there were several members who did not vote. It was purely an expression of opinion.

Then it was moved by Dr. Turner Z. Cason, of Florida, and discussed that the

Board of Governors recommend to the Board of Regents that a Committee be appointed to study this whole problem thoroughly again, and bring in a subsequent report. Someone pointed out that that had been going on since 1944, and I remarked that I thought that some day the Board of Regents would want the Board of Governors to make up their minds as to what it wants. The reply was "we want another year, and we would like to have this Committee study it thoroughly, and we, the Governors, would like to have another opportunity to express our opinions on it." I pointed out that the Regents had at the last meeting decided to appoint a Committee who would report at a meeting this coming autumn. The Governors however felt, Mr. President, that they would like to have another "go" at it before the Regents finally take action.

Was there anything else, Mr. Loveland?

MR. LOVELAND: There was another item that might be expanded upon, namely, the proposal by Dr. Edgar V. Allen's Committee of a year ago. You will recall that Dr. Allen's motion before the Board of Governors was to democratize the College and its methods of selecting Governors, Regents and Officers. He hoped to present a method of having the members elect their own Governors from their particular territories, the Governors possibly electing the Regents and the Officers. The Committee appointed by the Chairman of the Board of Governors reported to the Board, through its Acting Chairman, Dr. Benjamin F. Wolverton, of Iowa, and presented a very mild and perfectly harmless suggestion, by which the present system, as prescribed by the By-Laws, might be augmented through consulting the Fellows to a greater degree concerning the selection of the Governors, but in no way restricting the action of the Nominating Committee. The Board of Governors, however, as a whole, appeared suspicious of any proposal, and it voted down even this mild suggestion. They would have no part in changing the present system.

DR. WALTER L. PALMER: That is very properly stated, and the vote was at least three to one against the proposal. The Governors indicated very great fear of politics appearing if anything of that sort were adopted.

PRESIDENT PALMER: It has been suggested, and very properly so, that the Minutes of the Board of Governors' meeting shall be abstracted carefully and a copy sent to each member of the Board before we take up the several points which Dr. Palmer has brought up.

According to the Board of Governors, it would be proper that we appoint a Committee which would have on it representation from the Board of Governors to continue the study of the proposals of the Committee on Credentials.

DR. MAURICE C. PINCOFFS: Will this Committee deal exclusively with the proposal that Associateship be dropped, or with all aspects?

PRESIDENT PALMER: With all aspects, I think.

The next item is the selection of the 1950 meeting place. As you know, New York has already been selected for 1949. Will the Secretary report on some of the information we have gathered during a recent canvass of the Board of Regents?

MR. LOVELAND: Those who have been on the Board of Regents previously know that when the matter of selecting a city for 1949 came up, the schedule in various cities was very nearly filled, and they refused to hold open dates until the San Francisco Meeting; thus, the Regents had to be canvassed by mail, and after two or more such efforts, New York was selected for 1949. We are now requested to select our meeting place for 1950. It is quite apparent, under present conditions, that we must work two years ahead on the Annual Session.

The principle involved in the mail vote, which, perhaps, was not wholly understood, was whether the College should not alternate its Annual Meetings between the east and midwest, and occasionally the far west, or in Canada. It was thought that if New York were selected for 1949, the 1950 meeting might be held in the midwest; if the 1949 meeting went to the midwest, the 1950 meeting would be in the east.

Two of the chief contenders for the 1949 and 1950 meetings were New York and Boston. Boston wanted the meeting in 1950 and New York in 1949. In our final survey of the Regents, there were six who thought we should meet in New York in 1949 and in the midwest in 1950, adhering to our former plan of alternating the territory. There were only five who voted for St. Louis in 1949 and Boston in 1950, and of those six thought we probably ought to keep up the alternating plan. However, the significant thing was that thirteen of the Board said they would favor New York in 1949 and Boston in 1950, regardless of any alternating principle. They felt it not unfavorable for the College to meet twice as close together as New York and Boston. I think the President-Elect, Dr. Reginald Fitz, should speak about Boston for 1950. We shall be welcome in Boston, in Cleveland or in St. Louis. We might readily be welcome in Baltimore too, but there was so little interest in Baltimore expressed among the Regents that I have removed Baltimore from the list of contenders. Therefore, your consideration of the 1950 meeting place would have to be among Boston, Cleveland and St. Louis.

A new and interesting suggestion came up at this meeting—Dr. George F. Strong can speak on it. One of the newer Fellows, the Professor of Medicine at the University of Toronto, Dr. Ray Fletcher Farquharson, has expressed, through Dr. Strong, Dr. Harold A. Des Brisay, and some others here, an interest in Toronto in having the College come there some time. We have never held a meeting in Toronto; we have not examined their facilities yet, but I believe that the facilities are adequate, and I think it would be very valuable to the College to keep Toronto in mind for some later meeting.

Boston can provide the Mechanics Hall for meeting facilities; I have examined it and it contains adequate meeting rooms, exhibit space and other facilities; it is near the hotels, and while the building is old, it is certainly adequate.

Now in Cleveland and in St. Louis we would have fine Convention Halls. The rental expenses in Boston, using the Mechanics Hall, which is a private hall, would probably be a thousand or two thousand dollars more than at Cleveland or at St. Louis, where the cities for the most part provide the meeting halls. I feel, however, that we should be influenced more by the medical attractions of the cities.

Dr. Reginald Fitz: I have given this considerable thought, and I think the issue really depends on whether we feel it is proper to break away from the long standing tradition of the College to alternate geographically in its meeting places. There is no question about Boston putting on a particularly good show, because our hospital facilities are well integrated and the hospitals have large amphitheaters. I am sure Mechanics Hall would work well. The puzzling problem is, as Mr. Loveland pointed out, we have to think two years ahead, and we have to consider whether it would be wise to deviate from a long standing tradition. If it is, I am sure that Boston would work all right. It is curious that there is so very little expression of favor in keeping up the old tradition. On the other hand, what we want to do is to give everyone a chance to come to the meetings, and I would hate to run the risk of having Fellows not want to come to the east for two successive years, and I would like to hear it discussed.

Mr. Loveland: Another quite important consideration is that of who would be the General Chairmen in the various cities.

Dr. Ernest H. Falconer: Mr. President, I would like information. It is my impression that we haven't many members especially active in St. Louis and who are particularly anxious to have the College come there.

President Palmer: Dr. Ralph Kinsella is very active and would do a good job.

Dr. A. B. Brower: Mr. Chairman, I would just like to give you an impression that I have received from a number of Fellows in the middle west, merely for the purpose of conveying that expression of opinion. I know the opinion of a number of Fellows in Ohio, in particular, and the southern parts of Illinois and Indiana, who are a little bit touched about this business of having these things becoming more

regionalized. There are a number who would particularly like the meeting to be held in the middle west in 1950.

DR. HUGH J. MORGAN: I think we must consider the concentration of our membership. My guess is that the geographical distribution of the members is such that we need to have two meetings on the eastern seaboard to one in any other region of the country. Furthermore, I think the College should go where it best would be served in the terms of the Annual Meeting. One can get on an airplane in the morning and be anywhere in the country by the evening. It is absurd to think about the geographical location as a matter of convenience any more. I strongly favor our going to Boston on many accounts, and perhaps the most important being that I am sure we would have a perfectly grand program.

DR. LEROY H. SLOAN: I am in favor of Boston for 1950, but I think the College should also bear in mind the importance of the fact that it does something for a region when the College meets there, and it does something for the College. We should not lose sight of the fact that where we are weak we should become strong, and we can become strong by putting the Annual Sessions there. My own vote was for St. Louis in 1949 and Boston in 1950. Coming from the middle west, I am perfectly satisfied that it be Boston. We do not have to worry particularly about the geographical end of it, but I think after 1950 we ought to be a little careful about where the next succeeding meeting is to be held, so as not to de-emphasize regions.

To bring it to a head, I move that we meet in Boston in 1950.

DR. MORGAN: I second the motion.

. . . The motion was put to a vote and unanimously carried. . . .

DR. GEORGE F. STRONG: I hope the Regents will keep in mind this possibility of meeting in Toronto. It appeals to me as being properly classified as middle west. The College is not as strong in Canada, and particularly in Ontario, as it should be, and I know that a meeting there would do a great deal to build the prestige of the College, and I believe they could put on a good meeting. I hope that in 1951, or not later than 1952, we may look forward to a meeting there, provided the facilities are adequate.

PRESIDENT PALMER: With the increase in the size of our membership and the increased difficulties in getting larger cities to accommodate us, we might consider at some time the possibility of meeting once in a while at Atlantic City. It would be impracticable, perhaps, to give clinics at Atlantic City. On the other hand, my feeling is that the lectures have been very popular, and it might be possible to increase the lectures and the panels and to omit the clinics once in every so many years.

The next on our agenda is the authorization on behalf of the Regents for the President, General Chairman and the Executive Secretary to complete all necessary arrangements for the 1949 Annual Session.

. . . On motion by Dr. George F. Strong, seconded by Dr. Alex. M. Burgess, and unanimously carried, that authorization was granted. . . .

PRESIDENT PALMER: The Secretary has some communications.

MR. LOVELAND: Dr. William J. Kerr has handed me these two communications, and asked me to read both of them. They originate in the office of Mr. Daniel M. Wilkes, who was the publicist for our Committee on Publicity for this meeting. They have done a most excellent job, and they have included in these letters recommendations and statements concerning their experience.

. . . The Secretary then read the above mentioned communications. . . .

. . . On the motion of Dr. George F. Strong, seconded by Dr. Charles F. Tenney and others, and enthusiastically carried, the Board of Regents extended a special vote of appreciation to Dr. William J. Kerr and Dr. Ernest H. Falconer, General Co-Chairmen, for the very successful meeting in San Francisco. . . .

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary

AMERICAN COLLEGE OF PHYSICIANS, INC.

Balance Sheet, December 31, 1947

GENERAL FUND

Assets		
Current:		
Cash in Banks and on Hand		$ 74,749.36
Accounts Receivable:		
Drexel & Co.	$ 1,634.30	
Advertising	2,321.64	
Postgraduate Courses	420.00	
ANNALS Excess Illustrations	167.86	
American Air Lines	700.37	5,244.17
Inventory of Keys, Pledges and Frames, at Cost		477.55
Accrued Income on Endowment Fund Investments		1,521.64
Accrued Income on General Fund Investments		688.13
Investments at Book Value		156,076.42
Insurance Deposit		555.00
Total Current Assets		$239,312.27
Deferred:		
Expenses, 29th Annual Session	$ 5,171.02	
Advertising, Vol. XXVIII	7.46	5,178.48
Fixed:		
College Headquarters:		
Real Estate	57,728.45	
Less Depreciation	11,000.00	46,728.45
New Building Appropriation		55,000.00
Furniture and Equipment, at Cost	14,596.75	
Less Depreciation	11,151.23	3,445.52
Investment, Real Estate, 404-12 S. 42nd Street		9,170.50
		$358,835.22

Liabilities		
Current:		
Accounts Payable		$ 439.30
Building Reserve Fund		34,723.00
Deferred Income:		
Advance Subscriptions, ANNALS OF INTERNAL MEDICINE, Vols. XXVIII to XXXVI		31,263.21
Restricted Funds:		
Chicago Postgraduate Fund	$ 443.30	
Philadelphia Postgraduate Fund	2,284.30	
Building Alterations Fund	94.60	2,822.20
Reserve—Fellowship Fund		19,016.69
Total Current Liabilities and Funds		$ 88,264.40
General Fund, as annexed		270,570.82
		$358,835.22

ENDOWMENT FUND

Cash in Banks:		
General	$1,996.78	
A. B. Brower Fund	2,500.00	$ 4,496.78
Accrued Income on Investments		1,521.64
Investments at Book Value:		
General	256,788.11	
James D. Bruce Fund	10,000.00	266,788.11
(TOTAL ASSETS, $631,641.75)		$272,806.53

Endowment Fund, Principal:		
General	$258,784.89	
James D. Bruce Fund	10,000.00	
A. B. Brower Fund	2,500.00	$271,284.89
Accrued Income, Due to General Fund		1,521.64
(TOTAL LIABILITIES AND FUNDS, $631,641.75)		$272,806.53

Operating Statement

GENERAL FUND

For the Year Ended December 31, 1947

Balance, January 1, 1947		$234,159.26	
Less:			
Transfer to Endowment Fund of the Initiation Fees of Life Members	$ 6,920.00		
Adjustment of Dec., 1946, Advertising	2.16		
Transfer from 1946 Chicago Regional Meeting Surplus	191.62		
Transfer from 1946 ANNALS OF INTERNAL MEDICINE Subscription Overpayment	3.00	7,116.78	$227,042.48
Net Income for the Year Ended December 31, 1947, as Annexed			43,528.34
BALANCE, December 31, 1947			$270,570.82

ENDOWMENT FUND

For the Year Ended December 31, 1947

Principal Account, January 1, 1947		$223,373.89	
Add:			
Life Membership Fees received during 1947	$28,306.67		
Transfer of Initiation Fees of New Life Members from General Fund	6,920.00		
Transfer from Dues Account	70.33		
Transfer from Subscription Account	18.00		
Transfer from Initiation Fees Account	80.00		
Net Profit on Endowment Fund Investments	16.00	35,411.00	$258,784.89
JAMES D. BRUCE FUND:			
Principal, January 1, 1947 (no changes) (Income included in General Fund Statement for 1947)			10,000.00
A. B. BROWER FUND:			
Principal Received			2,500.00
TOTAL, Endowment Funds			$271,284.89
TOTAL, All Funds			$541,855.71

Summary of Operations for the Calendar Year 1947

Income:

Annual Dues			$ 53,516.25
Initiation Fees			15,538.67
Subscriptions, ANNALS OF INTERNAL MEDICINE			62,435.59
Advertising, ANNALS OF INTERNAL MEDICINE			26,246.07
Income from Investments, General Fund (including Accrued)			7,327.29
Income from Investments, Endowment Fund (including Accrued)			8,784.21
Dividend on Perpetual Insurance Deposit			60.00
Sale of 1947 Membership Roster			25.25
Postgraduate Courses, Balance			1,490.19
Rent—404–12 S. 42nd Street		$ 1,649.54	
Less: Maintenance	$ 303.42		
Light, Gas and Water	32.78		
Taxes	489.55		
Insurance (fire)	20.00		
Insurance	32.76	878.51	771.03

Profit from Sales of General Fund Securities		86.40	
Profit on Equipment Traded in		34.70	
Twenty-eighth Annual Session:			
Exhibits	$16,384.21		
Guest Fees	1,767.00		
Banquet Balance	200.49	18,351.70	
TOTAL INCOME			$194,667.35
Expenses:			
Salaries		39,652.17	
Communications		6,114.82	
Office Supplies and Stationery		3,417.84	
Printing		40,438.87	
Traveling Expenses (exclusive of Annual Session)		2,389.43	
Maintenance, Executive Secretary's Office		34.44	
Miscellaneous		2,037.73	
Research Fellowships		20,000.00	
College Headquarters:			
Maintenance	$ 3,932.99		
Heat, Light, Gas and Water	1,072.25		
Insurance	89.93		
Taxes	170.77	5,265.94	
Depreciation on Building		1,000.00	
Depreciation on Furniture and Equipment		607.86	
Keys, Pledges and Frames		163.24	
John Phillips Memorial Prize		252.46	
Twenty-eighth Annual Session:			
Publicity Committee	$ 516.00		
Ladies' Entertainment Committee	1,001.24		
"Harvey," Harris Theater	510.25		
Convocation	926.61		
Governors'-Regents' Dinner	518.24		
Salaries	7,119.66		
Communications	747.45		
Office Supplies and Stationery	201.72		
Printing	3,186.85		
Traveling Expenses	5,740.54		
Miscellaneous	3,018.99	23,487.55	
Investment Counsel Service		250.00	
Security Custodian's Fee		398.00	
Employees' Pension Fund		2,254.77	
Collection and Exchange		372.14	
1947 Supplement		767.96	
Regional Meetings		2,233.79	
TOTAL EXPENSES			$151,139.01
Net Income for 1947 Credited to General Fund			$ 43,528.34

These financial data taken from the official Auditor's Report.